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SCIENCE

29 December 1961
Vol. 134, No. 3496

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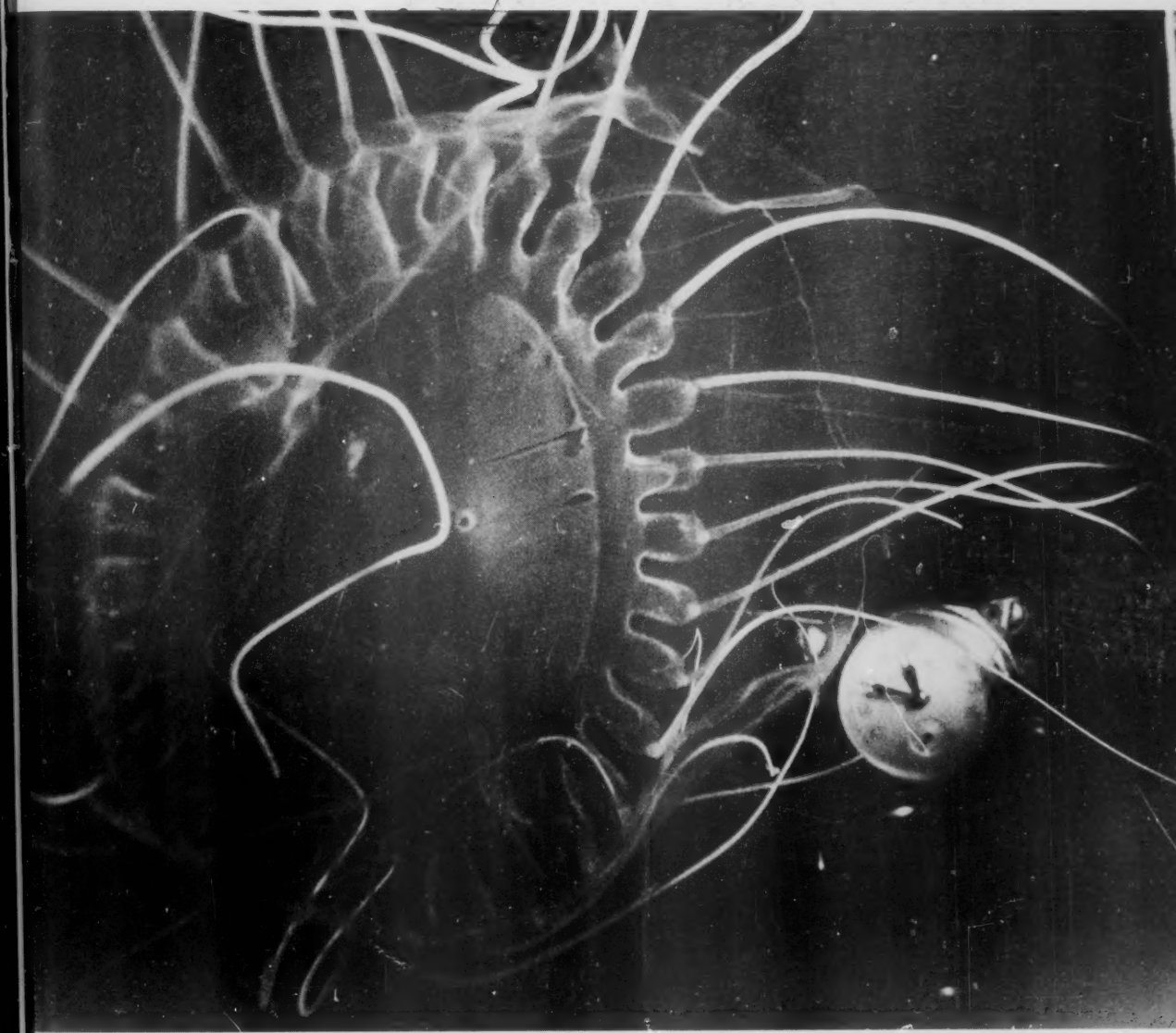

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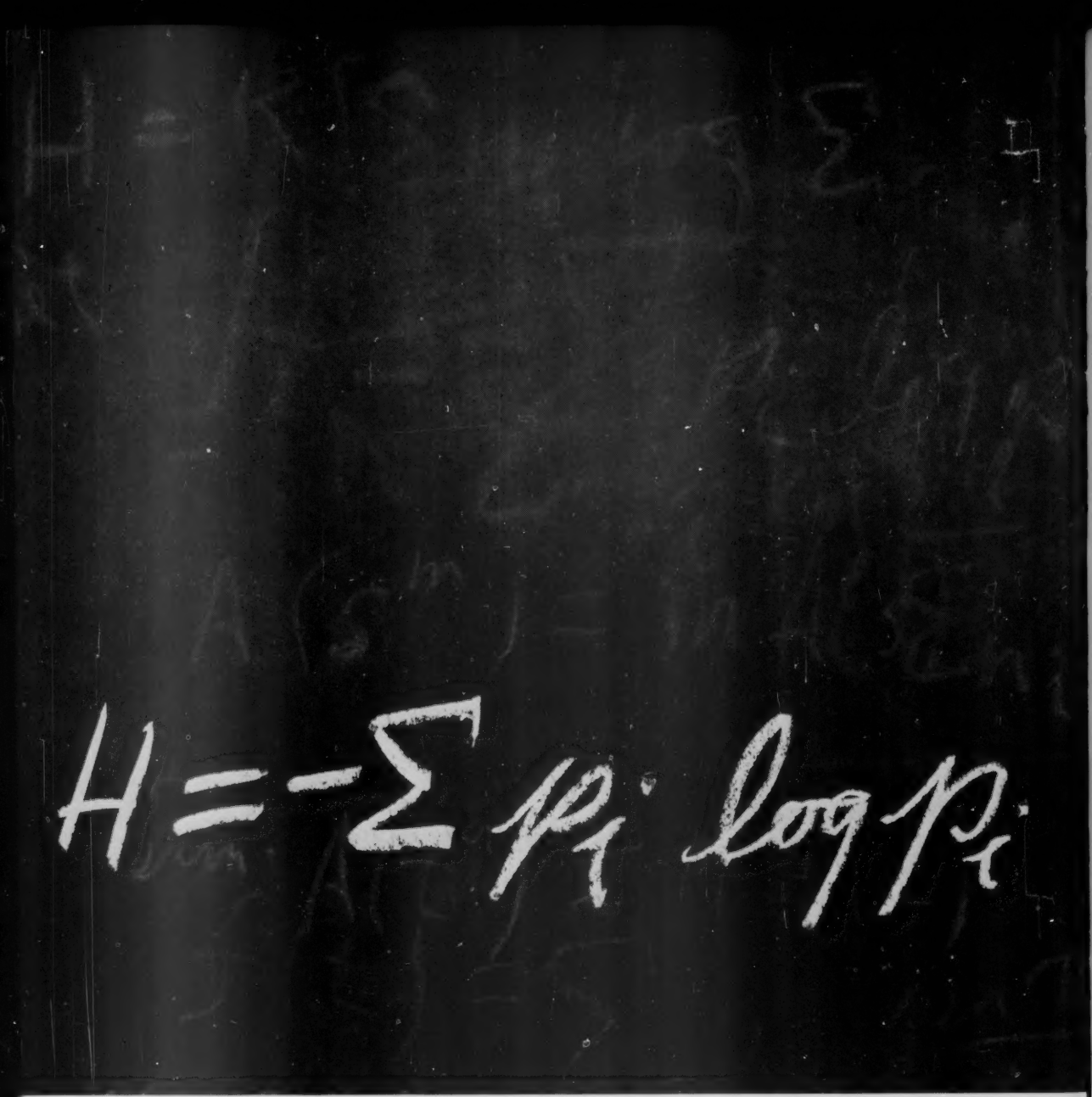

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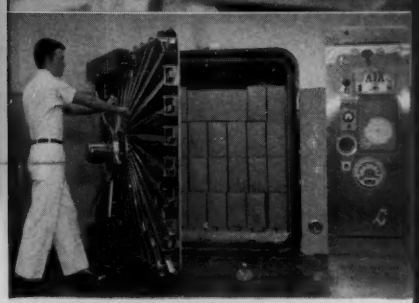

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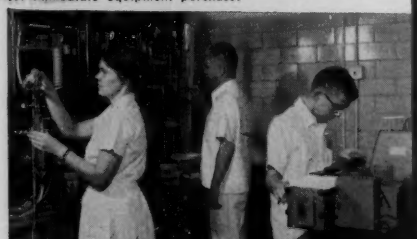

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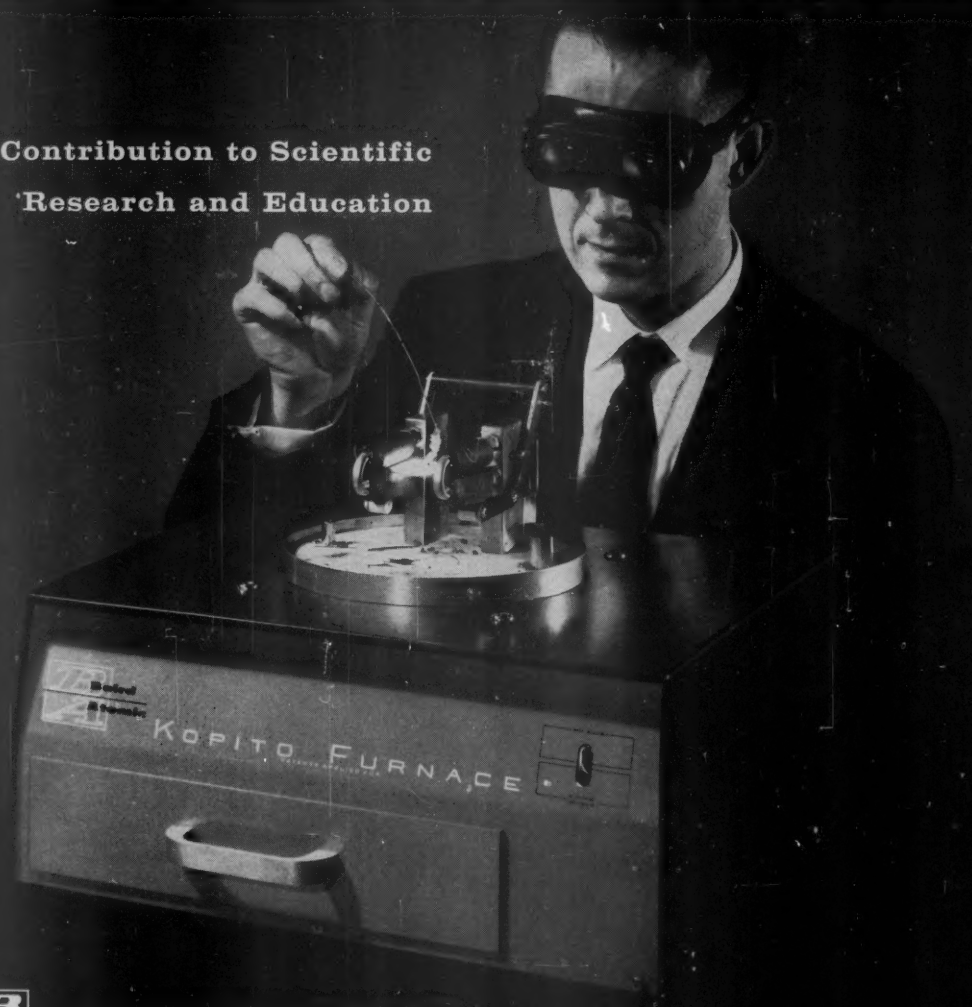

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29 December 1961, Volume 134, Number 3496

SCIENCE

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Self-portrait of rare jellyfish *(Solmissus incisa)* taken at a depth of 1000 meters off George's Bank during studies of bioluminescence in the sea. When this 12-centimeter medusa drifted into the range of the camera (designed by Breslau and Edgerton), its luminescence was picked up by a phototube, which triggered an electronic flash to take the picture. The 2-centimeter watch gives both scale and the exact moment of exposure. [George L. Clarke, Harvard University and Woods Hole Oceanographic Institution]

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A new Van de Graaff accelerator has appeared on the scene. It did not spring full-blown from the brow of an inspired design engineer and, in fact, bears a remarkable resemblance to its predecessors. It evolved rather from both an inspired customer's need and improved state of the art. The KN-4000, at *4 Mev*, does fill in a gap in the voltage range of standard equipment. It offers great versatility of use, low installation cost, and delivers a very respectable *400 μa* of current at rated voltage. A convertible machine, it will also accelerate a full milliampere of electrons (*4 kilowatts*).

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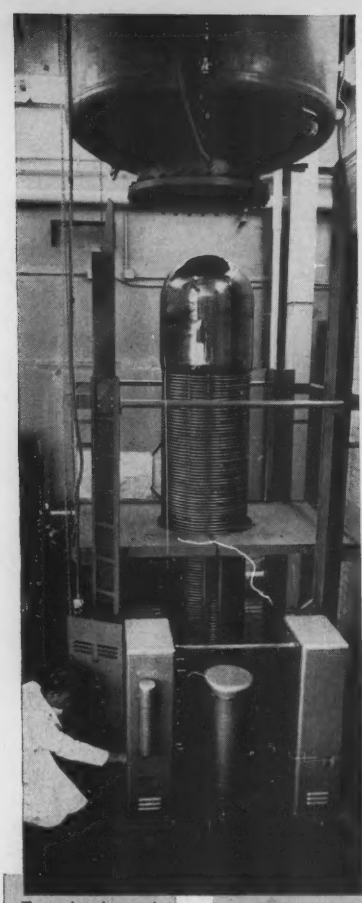

Terminal and accelerating section of the KN-4000 Van de Graaff with pressure tank removed.

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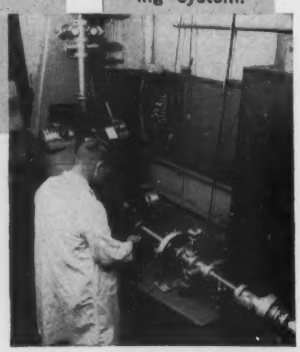

Short-lived radioisotope production and neutron activation, radiation effects and solid state work, radiobiology, energy level determinations, and (with conversion) massive-dose studies, catalysis and polymerization are a few of the possible areas of use. An English producer of medical supplies will use the 4 kw electron output for sterilizing his product in bulk quantities. A U.S. university will use KN-4000 as a central tool in neutron physics.

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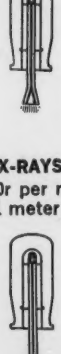

POSITIVE IONS
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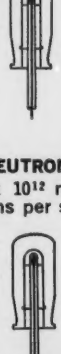

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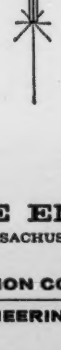

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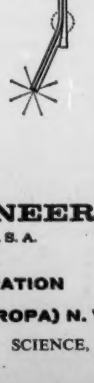

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The Twelve-Pound Book

When this number of *Science* is published we will have barely room enough in our binder for volume 134 (July to December) to squeeze it in. Last year we had the same problem, so we enlarged the binders to take care of the expected growth. But we are at the end of that road, for larger binders than we used this year are not available. Even if they were, we would hesitate to use them, since the current volume and its binder will make an unwieldy twelve-pound book. We have adopted an obvious expedient: in 1962 we will publish four instead of two volumes.

For *Science*, the last few years have been notable for growth in circulation as well as in physical size. Both phenomena are in part attributable to the combination of the *Scientific Monthly* with *Science* in January 1958. It is instructive to compare *Science* in the year now ending with *Science* in 1957, the year before the combination. The following increases have occurred: circulation, from 38,000 to 71,000 (87 percent); number of editorial pages, from 1836 to 2502 (36 percent); number of advertising pages (in the face of annual increases in advertising rates), from 896 to 1686 (88 percent); gross advertising revenue, from $264,000 to about $800,000 (230 percent); total number of pages, from 2732 to 4188 (57 percent). Two-thirds of the increase in the number of editorial pages is attributable to the greater space devoted to leading articles, which went up in number from 101 in 1957 to 134 in 1961 and in number of pages from 449 to 811 (81 percent), and to letters, which went from 15 to 94 pages.

If we focus our attention on the differences between 1961 and 1960, we find that both circulation and advertising volume have climbed at a rapid rate: circulation went from 63,000 to 71,000 (13 percent); advertising pages from 1403 to 1686 (20 percent); and total pages from 3842 to 4188 (9 percent).

The growth in circulation is gratifying, but the growth in size gives us concern. How big should the weekly issues become? Our staff thinks that we have approached what should be our limit in those issues that once a month carry the customer's service or "bingo" card so dear to advertisers. Accordingly, we plan two steps. For one thing, as soon as the machinery for processing returns can be set up, we shall put "bingo" coupons in the 40 issues that do not contain the cards. If readers will use the coupons, advertisers may be more willing to use the smaller issues and thus reduce the peak loads. Secondly, we have put an upper limit on the amount of advertising that may appear in any number except the *Instrument Issue*.

As advertising increases, so should the amount of editorial material. We think it desirable that the editorial material should make up not less than about 42 percent of the total pages in any issue. Thus, if advertising should continue to increase, despite the rise in rates which takes effect next month, *Science* would continue to grow at a rate of about two pages of text for each additional three pages of advertising accepted.

We hope that the steps we plan to take will result in issues of more equal size and that at some not too distant time our annual growth in size will become asymptotic. So much for the mechanical problems we can foresee. They could be worse.—G.DuS.

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29 December 1961, Volume 134, Number 3496 SCIENCE

The Scientific Status of Pharmacology

Through pharmacology, a subject of ancient interest but a young science, important generalizations are emerging.

Chauncey D. Leake

Current custom suggests that the retiring president of the American Association for the Advancement of Science give an informal, informative, and interesting review of the status of his professed scientific discipline. This custom is tough on me. As a scientist, I make pretense at being a physiologist and a pharmacologist. On the other hand, I am humanistically interested in the history and philosophy of science. It may be that I can combine these interests and say something that will be appropriate on the history and philosophy of physiology or pharmacology (*1*).

Since pharmacology is currently attracting so much attention, what with congressional hearings and spectacular business developments, it would seem appropriate to consider what pharmacology is about. What is the scientific status of pharmacology? What are the characteristic and unique features that distinguish it from other sciences? What are the theoretical concepts on which pharmacology, as a science, may rest? It what ways may pharmacological knowledge be applied in a worth-while way to human welfare?

It is helpful occasionally to examine the basic concepts of an intellectual scientific discipline and to explore its theoretical foundations. This is becoming increasingly important in the biological sciences. Apart from such great theoretical generalizations as the principle of evolution, the biological sciences are not as satisfactorily explored from the standpoint of theoretical background as the physical sciences are. The significance of the theoretical development of the physical sciences is clear when one considers the many dilemmas confronting us in regard to nuclear power. It has been the *applications* of mathematical, physical, and chemical theory which have made possible so much of our current comfort and so many of the conveniences of civilization.

Americans generally seem to be reluctant to undertake basic theoretical studies. However, if we are to maintain any satisfactory world position in the applications of science to human welfare, we must always supply some of the essential theoretical nourishment on which practical applications thrive. The essential food for our very practical culture is scientific theory. So it would seem helpful to give some attention to the theoretical aspects of pharmacology.

Most people who are concerned with pharmacology are interested in it as a practical matter by which new drugs may be developed, some of which may be very important, saving many lives, promoting much health, and incidentally bringing in much money to those who are responsible for the development and use of these drugs. The great drug industry itself might benefit from taking a hard look at some of the theoretical bases on which pharmacology may rest.

In order to assist in an appreciation of the current status of pharmacology, my discussion will deal in turn with its traditional background (protopharmacology), the origin of its fundamental scientific problems, an analysis of the factors influencing the intensity of drug action, and finally a consideration of its practical applications. Apologies are offered in advance for what may seem to be dogmatic assertion on the one hand, or overemphasis of trivialities on the other.

Protopharmacology

Pharmacology is a subject of ancient interest, but it is a relatively new science. Pharmacology is the study of the interaction of chemical agents (drugs) with living material, whether the action is good or bad for the living material, or whether the living material is plant or animal in origin. If the action is harmful to living material, the field of inquiry is called toxicology and the action of the chemical is said to be "toxic."

The Greek-derived term *pharmacology* comes from *pharmacos*—something to be cast out, a harmful thing, a scapegoat—and *logos*—the word, or the truth about, or (as we indicate now) the study of. *Toxikon* means a poison or a poisoned arrow.

These distinctions between the possible useful action of a drug and its possible toxic effect were recognized anciently. Peoples everywhere on earth tried the plant, animal, and mineral materials in their environment for possible use as food, and as a result they noted what the actions of these materials may be. Many observations were also made on what animals eat in their environ-

The author is professor of pharmacology, Ohio State University, Columbus. This is the text of his address as retiring president of the AAAS, delivered 28 December at the Denver 1961 meeting.

ment. In these ways, many of the plant purgatives came into use, as well as natural products for expelling worms, relieving pain, producing exaltation, or treating bruises.

There seem to have been many keen associations in these ancient observations. The old Egyptians, as indicated in the Ebers papyrus, written around 1550 B.C., recommended that moldy bread be applied to skin bruises. It took around 3500 years of social development before penicillin was finally derived from molds.

Folklore about the action of crude drugs has accumulated for centuries. This rough information was applied chiefly to the relief of symptoms of disease. From the medical folklore of all primitive peoples, through the old Egyptian medical papyri, through the magnificent compilation of Nero's surgeon Dioscorides, through the writings of Galen (A.D. 130–200), Avicenna (980–1037), and the medieval compilers, and through the Renaissance herbals and the complexities of the 18th-century pharmacopeias this empirical method continued. It probably began with chance observations on the gross effects of plant, animal, or mineral materials as they may have been tried for food, or as they may have come into contact with the skin. The Ebers, Hearst, London, and Berlin Egyptian medical papyri, dating from around 1500 B.C., contain hundreds of prescriptions which seem to be quite natural applications of such chance observations to the relief of the symptoms of various diseases.

These Egyptian medical papyri represent the earliest compilations of empirically obtained and empirically applied pharmacological knowledge. They are composed on the basis of rough classifications of diseases to be treated, and they recommend prescriptions for such diseases on the assumption that the diagnosis has been made. The folklore of all peoples is rich with similar material, but in comparison with the Egyptian medical papyri, the medical lore of other peoples is not as well organized, codified, or conventionalized, particularly with respect to dosage, to detailed directions for preparation and administration, or to combinations (polypharmacology).

Complex prescriptions containing many ingredients probably developed in the process of compilation and transcription of medical writings when the compiler was trying several materials recommended for the same purpose, with no indication of their relative effectiveness. What would be more natural than to combine them all in the same prescription? This tendency reached its climax among the Arabian compilers of the Middle Ages, such as Avicenna, and the mysterious Mesue, who attempted to condense the vast accumulation of medical recipes from ancient Egypt, the extensive Coptic literature, and the Greco-Roman writers.

On the basis of medical application of the botanical work of Aristotle's pupil Theophrastus (370–286 B.C.), Dioscorides, in Nero's time, originated a different system. This was to describe as carefully as possible the individual crude materials of plant, animal, and mineral origin as used in medicine, so that they might be identified, and then to indicate how each was to be prepared and administered and for what purpose each was to be used. This method of organization, on the basis of the materials used rather than of diseases to be treated, was subsequently followed in the development of modern pharmacopeias. The earlier formulary type of reference continued, however, and is currently exemplified in such a volume as the popular *Merck Manual*.

Pharmacopeias, or reference books of standardized and legally authorized medicinal preparations, arose in the 16th century. They met the obvious need of making uniform the various modifications of the same recipe made by different apothecaries. They thus enabled physicians ordering various formulas to expect some reasonable degree of uniformity in the preparations used, so that there might be some resulting uniformity in the effect produced in response to dosage.

A fundamental problem of pharmacology, the relation of dosage to effect, was thus recognized. This problem was early implicit, especially in poisonous materials. Even though three-fourths of the crude drugs recommended for oral use in the old Ebers medical papyrus were quantitated, no toxic dosages were ever recommended.

As the art of distillation was taken over by the medieval alchemists from the Arabs, the standardization of drugs again became important, in the production of "elixirs"—those pleasant but temporary answers to the pathetic quest for eternal youth. The rebellious Paracelsus (1493–1541) also aided in the development of standardization of drugs by popularizing "tinctures," and by using relatively simple preparations of such substances as sulfur, arsenic, and iron. The intricate letter of the famed anatomist Andreas Vesalius (1514–64) on the "China Root" (1546) was also influential in emphasizing the need for drug regulation and standardization.

The first real pharmacopeia was the formulary authorized by the Senate of the City of Nuremberg. It was compiled by the brilliant youngster Valerius Cordus (1515–44) and was published in 1546. This example was soon followed in other European centers, and physicians were now able to prescribe preparations of uniform composition. The important principle was realized of furnishing a standardized and uniform complex formula under a relatively simple name. By specifying standards for the ingredients and for the methods of compounding, the pharmacopeias made it possible to detect adulteration, and thus to protect on the one hand against ineffective materials and on the other hand against toxic effects from overdosage with unknown amounts of dangerous drugs.

Sporadic experiments began to be made for the purpose of studying the action of drugs on animals. These experiments were usually undertaken to test suspected toxic action. Thus, in 1676 Johannes Wepfer (1620–95) demonstrated nux vomica tetanus in dogs. The introduction of many new and exotic drugs from the New World in the 17th century stimulated much experimentation on crude preparations. The experiments seem chiefly to have been made in order to get some idea as to the possible toxic dosage of such strange drugs as tobacco, nux vomica, ipecac, cinchona bark, and coca leaves.

By the 18th century many such systematic studies were being made. Anton Störk (1731–1803) critically examined the actions of hemlock, stramonium, aconite, and hyoscyamus. An extensive toxicological survey (1765) by Felice Fontana (1730–1805), in which more than 6000 experiments were made, led him to the fundamental opinion that general symptoms of drugs are produced by actions on particular organs. Thus was the way prepared for modern pharmacology.

Development of Pharmacology as a Science

Pharmacology as a significant science could not develop until the rise of modern chemistry at the end of the 18th century, largely under the influ-

ence of the French martyr A. L. Lavoisier (1743–94). By that time it had become possible to obtain pure chemical compounds of unvarying physical-chemical properties. Some could be synthesized by the beginning of the 19th century. Methods then became available for the isolation, in chemically pure form, of biologically active principles from crude drug sources. The contributions of the great 18th- and 19th-century chemists made modern pharmacology possible.

Yet it should be noted that relatively pure inorganic compounds had already been empirically introduced in medical use, especially such saline purgatives as potassium sulfate (Paracelsus) and sodium sulfate (J. R. Glauber, 1604–88). Chemical elements had already been used, as in the remarkable Arab ointment containing mercury which was used for skin conditions and which later became so important in the treatment of syphilis as soon as that scourge was recognized, at the close of the 15th century. Elemental sulfur had also early been used medically.

The credit for being the first to isolate a chemically pure active principle from a crude drug should go to Friederich W. Sertürner (1783–1841). He reported his studies from 1803 to 1817. From opium, the old pain-relieving crude drug, which is the dried latex from excised unripe poppy-seed capsules, Sertürner obtained, by ammonia precipitation, a white crystalline substance which he found to be a powerful pain-relieving and sleep-producing agent. This he named morphine, from Morpheus, the Greco-Roman deity of sleep. By direct experiments in animals and on himself, he found that the new substance is effective in very small dosage. Since he found no other agent in opium which causes the same sleep-producing and pain-relieving effects, he concluded that the valuable medicinal properties of opium are due to the presence of this substance.

Sertürner's discovery stimulated the development of a new scientific approach to pharmacology; with chemicals of constant physical properties available for the first time, dosage could be measured accurately in terms of mass of chemical per mass of living tissue, and the concept of a quantitative relationship between drug dosage and biological effect could be developed. Practically, this is important in medical practice, but physicians were slow to grasp its significance.

In theoretical application, it was

François Magendie (1783–1855), pioneer experimental pharmacologist.

seized upon by the French, probably under the influence of Gay-Lussac (1778–1850) and that handsome and inspiring teacher François Magendie (1783–1855). Within a few years, the latter, with Pierre Pelletier (1788–1842) and J. B. Caventou (1795–1877), had isolated emetine from ipecacuanha root, strychnine from nux vomica bean, and quinine from cinchona bark. Thus, the new and exotic plant remedies from the New World were brought under scientific control in the Old World. Soon Magendie issued a pharmacopeial formulary (Paris, 1821), based entirely on pure chemical agents. Official pharmacopeias slowly followed this example. The useful current *Merck Index* is of this sort.

These same methods of analysis and subsequent critical study were followed with respect to all sorts of crude drugs and are now being extensively applied to the conventionalized crude drug lore of China and India. The distinguished American pharmacologists K. K. Chen and C. F. Schmidt introduced ephedrine from the anciently used Chinese drug mahuang *(Ephedra vulgaris)*, for the treatment of asthma. Indian and Swiss pharmacologists introduced reserpine as a tranquilizer from the anciently used serpent root, which even Dioscorides had recommended as a remedy for quieting patients in a frenzy. Currently, also, the intricate complexity of initial crude preparations of "hormones," "vitamins," "enzymes," "coenzymes," and even "viruses" and "genes" are yielding to a similar technique. This will go on to include "vaccines" and other immunological preparations.

A recent dramatic example of the rapid isolation and identification of a biologically active compound from natural sources is afforded by the international study of quinones in electron transport. Enzyme studies on mitochondrial fractions involved in biological oxidation led Wisconsin scientists to discover that these active agents are quinones. Studies in England on coenzyme factors related to vitamins A and K led to the same conclusions. Further fractionization in commercial drug laboratories in Switzerland and the United States showed that these quinone coenzymes have terpene side chains and are found extensively in all kinds of living material. Soon it was recognized that these agents may be involved in photosynthesis. By means of the new techniques of chromatography, spectrophotography, and nuclear magnetic resonance, the specific chemical structure of these compounds was established within 4 years after their existence was first suspected. The one most widely found in nature is appropriately called "ubiquinone," and since it is a coenzyme essential for growth and repair of living material, it is highly likely that appropriate pharmacologic studies will establish clear indications for its possible usefulness in medicine or some other aspect of applied pharmacology.

A notable further development occurred when attempts were made to improve on the naturally occurring materials. These attempts began with the rise of structural organic chemistry. The high price of quinine and the great demand for it in the mid-19th century led to the synthesis of a number of valuable antipyretics and analgesics whose structure was affirmed by the evidence existing for that of quinine. The recognition of Kekule's then newly proposed ring structure in such complex chemicals as quinine and salicin (from willow bark, anciently used in the treatment of arthritis) prepared the way for the synthesis of salicylates. Then the discovery that acetylation of an organic compound would frequently reduce its toxic biological action led to the development of aspirin, the most widely used of all present-day drugs, apart from alcohol.

Willstätter (1872–1942) revealed the chemical structure of cocaine, isolated from coca leaf in 1856 by F. Wöhler and introduced as a local anesthetic by Carl Koller, of Vienna and later of New York, in 1884. Knowledge of the chemical structure of a natural product made possible synthesis for the desired purpose of obtaining substances less toxic and more efficient than the natural product. Cocaine is an excellent local anesthetic, but it produces addiction, as

was so dramatically recognized by the great American surgeon William Halsted (1852–1922) when he became addicted to its use as a result of contact with it in surgical practice and then courageously freed himself from the addiction. Willstätter's work with cocaine made it possible for synthetic organic chemists to make a flood of new local anesthetics less toxic than cocaine, free from its addictive properties, and often more efficient than the parent compound.

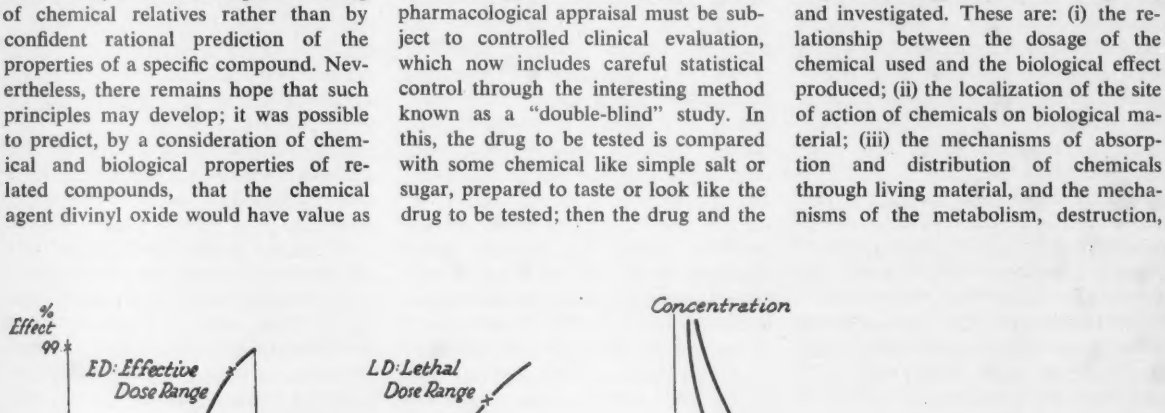
While a consideration of the relationship between chemical constitution and biological action or "biochemorphology," is fundamental in such efforts as these, few satisfactory generalizations or theories have been developed as guides in this field. Results are still achieved by laborious empirical testing of chemical relatives rather than by confident rational prediction of the properties of a specific compound. Nevertheless, there remains hope that such principles may develop; it was possible to predict, by a consideration of chemical and biological properties of related compounds, that the chemical agent divinyl oxide would have value as an inhalation anesthetic agent even before the compound had been prepared or was known.

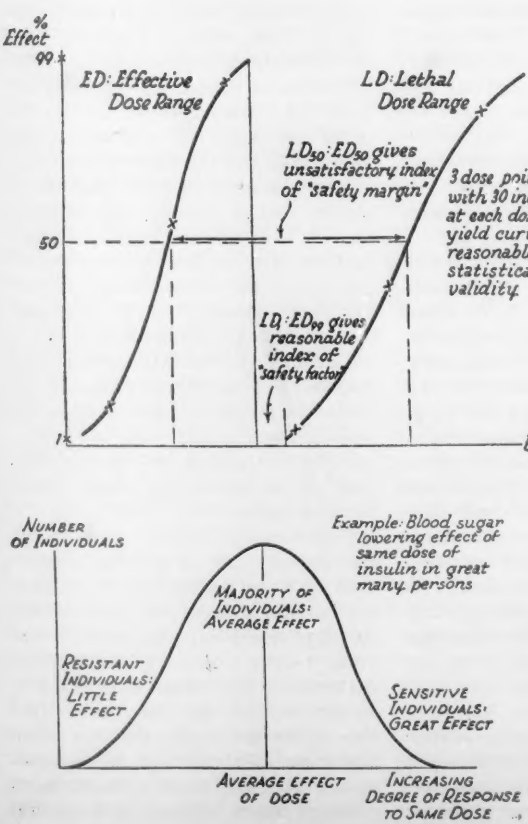
The steps in a characteristic pharmacological sequence are as follows: (i) the recognition of the biological activity of a crude preparation, from which (ii) the biologically active substance is eventually isolated in chemically pure form, free from all contaminating material, so that its physical properties are constant and determinable; then, (iii) the establishment, painfully, of the chemical structure of the substance; next (iv) the synthesis of its chemical relatives; then, (v) the laborious pharmacological appraisal of all the related compounds; and then finally, (vi) the choice of the one best suited for the particular application one has in mind.

To be applicable to medicine, this pharmacological appraisal must be subject to controlled clinical evaluation, which now includes careful statistical control through the interesting method known as a "double-blind" study. In this, the drug to be tested is compared with some chemical like simple salt or sugar, prepared to taste or look like the drug to be tested; then the drug and the other compound are given to equal numbers of patients with the same disorder, without either the attending physicians, the nurses, or the patients themselves knowing what each patient is getting. With studies of this sort, it is not surprising to get scientific confirmation of the anciently recognized fact that the attitude of physicians toward their patients may profoundly influence the effect of the drugs they use: patients tend to get well with hope and gentle treatment, regardless of the drugs that may be given to them.

Scientific Problems Involving Pharmacology

Gradually the fundamental problems of pharmacology have been recognized and investigated. These are: (i) the relationship between the dosage of the chemical used and the biological effect produced; (ii) the localization of the site of action of chemicals on biological material; (iii) the mechanisms of absorption and distribution of chemicals through living material, and the mechanisms of the metabolism, destruction,


% Effect
99
50
1
ED: Effective Dose Range
LD: Lethal Dose Range
LD50: ED50 gives unsatisfactory index of "safety margin"
3 dose points with 30 individuals at each dose will yield curves of reasonable statistical validity
LD1: ED99 gives reasonable index of "safety factor"
Dose
Concentration
A
B
Lethal Range
Effective Range
Time - Safety Factor at Concentration A
Time - Safety Factor at Concentration B is Indefinite


Number of Individuals
Example: Blood sugar lowering effect of same dose of insulin in great many persons
Majority of Individuals: Average Effect
Resistant Individuals: Little Effect
Sensitive Individuals: Great Effect
Average effect of dose
Increasing Degree of Response to Same Dose

(Top left) Relation of dose to percentage effect. (Top right) Curves showing time-concentration relationships during inhalation of an anesthetic. (Left) Curve showing the relationship of the number of reacting persons to the graded response to a given dose of a drug. Such dose-effect relationships were first firmly established by the English mathematician J. W. Trevan in his classic report "Statistical methods for estimation of biological variations in toxicity determinations," published in 1927.

or removal of drugs from living material; (iv) the specific mechanism of particular drug action; and (v) the relationship between chemical constitution and biological action.

Dose-Effect Relationships

Even in antiquity it was realized that there is a relationship between the amount of a drug that is given a person and the intensity of its effect. This dose-effect relationship was implicitly sensed for several millennia before any attempt was made to quantitate it. Indeed, the solid establishment of pharmacology as a quantitative science did not come until 1927, when the English mathematician J. W. Trevan (1887–1955) wrote his classic report on "Statistical methods for estimation of biological variations in toxicity determinations." Trevan was a consultant for a well-known drug company in London and had much to do with the development of methods for biological assay and standardization.

Trevan showed that there is a Gaussian distribution of variations in the intensity of response of biological material to a given dosage of a drug, and that if these intensities are summated for increasing dosage in accordance with the percentage of the total number of living specimens responding, the resulting relation is sigmoid if expressed graphically. Many refinements are possible with this sort of graphic representation, but the essential features were established by Trevan and extended by A. J. Clark (1885–1941). Clark not only analyzed various aspects of the dose-effect relationship but also established quantitation in time-concentration relationships. Time is an extremely important biological factor, but it may be neglected unless it is specifically emphasized.

It is rather remarkable that it took so long for a firm scientific basis to be provided for such an ancient idea as the relationship between a dose of a drug and the effect it might produce. There still remain many aspects of dose-effect and time-concentration relationships which are not ordinarily understood by those who may employ chemicals for biological effect (whether physicians, dentists, or members of the other health professions), or by agriculturists, or indeed by scientists in general. The matter is of practical importance when a physician tries to evaluate the relative merits of similar chemical agents which may be recommended for the same purpose. The "safety factor" is involved. The idea is to develop a drug with as wide a spread as possible between the dosage which will produce the effect desired and the dosage which may produce some unwanted, even lethal, effect.

Even for scientific purposes, drugs are frequently compared on the basis of the ratio between the dosage which will produce 50 percent of the effect desired and the dosage which may kill 50 percent of the samples of living material. This is the familiar ratio of ED_{50} to LD_{50}. In a practical way, however, no physician is interested in the dosage which will give the effect he desires in only half his patients, and certainly no physician in his right mind gives a rap about the dosage which will kill half of his patients. Much more significant, practically, is the relationship between ED_{99} and LD_1. However, since this is not as readily obtained by experimental methods, new drugs are often introduced clinically on the basis of a "safety factor" represented by the ratio of ED_{50} to LD_{50}. This is dangerous.

Those who use chemicals to produce an effect on living material are concerned with the factors which determine the intensity of activity. These factors can be expressed in a shorthand manner:

$$I=(f)\ D\frac{rA}{rE}, P, S$$

This statement indicates that the intensity of action of a chemical on biological material is determined by dosage (D) in terms of mass of chemical per mass of living material; the ratio of the rate of absorption and distribution of the chemical through the living material (rA) to the rate of detoxification or excretion of the chemical from the living material (rE); the physical-chemical properties of the chemical (P), which really determine the activity of the chemical on living material; and then (S), the specific and peculiar characteristics of the living material concerned, including its organizational status (in terms of macromolecules or ecological milieus), its age, its metabolic state, its "allergic" sensitivity, its pathological status, and such integrating factors as enzyme systems, neurohormonal systems, and sex.

It is clear that there may be quite precise quantitation of such factors as dosage, rates of absorption, distribution, detoxification and excretion, and physical-chemical properties. These factors are capable of precise scientific study, with results that may be expressed quantitatively. The product of dosage and the ratio of the rate of absorption and distribution of a drug to the rate of detoxification and excretion will give the concentration of the drug in the living material involved at any specific time after its administration. It is this concentration, with its mass action effect, which is a predominant factor in drug action.

A. J. Clark (1885–1941), pioneer in pharmacological theory. The photograph, taken in Edinburgh in 1938, shows a case of arrow poisons collected by Clark's predecessor, T. R. Fraser.

On the other hand, because of the peculiarities of the specific living material concerned, many judgment factors are involved. The application of pharmacology to medical affairs involves the judgment of the clinician and is a matter of long experience and wisdom. We are beginning to realize that similar judgment factors are involved in applying pharmacological knowledge to such aspects of living material as are involved in social organization or ecological milieus.

Localization of Drug Action

Magendie and his keen pupils in Paris began the study of the localization of the place of activity of newly isolated chemicals in living material. Because of general orientation toward eventual human use, these experimental studies were mostly carried forward on mammals. The study of the localization of the place of action of chemicals in the complex mammalian organism followed naturally from a considera-

A bronze memorial at the Collège de France, Paris, of Claude Bernard (1813–78), pupil of François Magendie and pioneer in the study of mechanisms of drug action. This photograph was taken in 1938; the statue was reputedly melted by the Germans in World War II.

tion of the symptoms of acute poisoning, as suggested experimentally by Fontana with crude drugs. It was promptly extended by J. E. Purkinje (1787–1869) in skillful experiments on himself, and by Claude Bernard (1813–78), Magendie's brilliant pupil. Bernard showed that the exotic Amazonian arrow poison, curare, which paralyzes animals when arrows tipped with it are shot into them, acts by blocking the transmission of the nervous impulse from motor nerves to muscles.

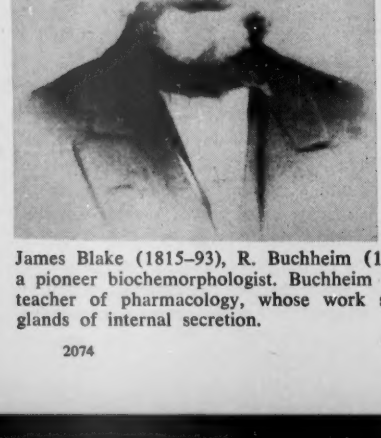
Since cells are considered to be the usual units of living material, and since molecules are taken as the units of chemical agents, it might be thought that pharmacology as a science would be chiefly concerned with the study of the interactions of molecules and cells. Indeed, about three decades ago this approach was carefully explored by A. J. Clark. While his study focused attention on pharmacology as an emerging quantitative science, the approach was clearly unsatisfactory, since molecules of chemical compounds can merely react with molecules of other chemical compounds. Actually, Clark's study showed that the amounts of drugs which are biologically active can be so small in some cases as to provide merely the possibility of activity of a single molecule of the drug on a single small isolated spot on the surface of a cell. These "active patches" have gradually been termed "receptors," and currently there is much study of the chemical characteristics of these highly localized areas on cell surfaces, at which chemical molecules may react. If molecules of drugs penetrate cells, it is to be expected that they will either interact with molecules within the cells, and thus disturb cellular activity, or interact with various aspects of the integrative mechanisms of cells, which probably are physicochemically based, and thus again alter the ordinary activity of the cell. Currently, it is recognized that there is a high degree of specificity of receptor sites on the surfaces of cells.

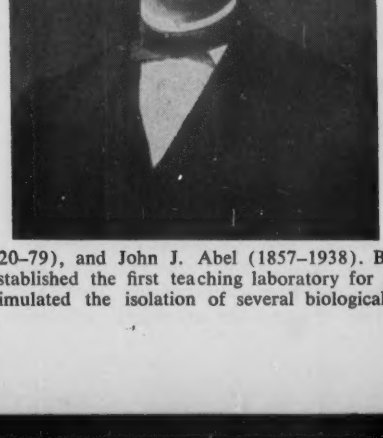
Drug Absorption and Detoxification

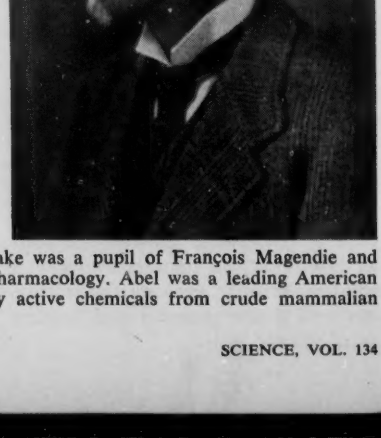
The important pharmacological problem of the mechanisms of absorption and detoxification of drugs was first investigated, in part, by Magendie but was systematically explored by Oswald Schmiedeberg (1838–1921) and J. von Mering (1849–1908). This became the special interest of M. von Nencki (1847–1901), and the study is being well extended currently by many brilliant investigations on pathways of absorption and detoxification. Many of these studies on the changes occurring in the chemical structure of drugs in contact with living material have revealed important metabolic pathways and enzyme systems. Tracing the direct avenue of absorption and metabolism of a drug has been made possible by extensive use of radioactive isotopes in key parts of the drug structure. The difficult matter of explaining how large molecules get inside cells and thus influence cellular activity seems partly to be explained by the process of pinocytosis, or "cell-drinking," as first described by Warren Lewis (1870–).

Mechanisms of Drug Action

Meanwhile, the practical achievements of Crawford Long (1815–78), W. T. G. Morton (1819–68), and J. Y. Simpson (1811–70) in demonstrating successful anesthesia for surgery by the use of ether and chloroform focused attention on the problem of the specific







James Blake (1815–93), R. Buchheim (1820–79), and John J. Abel (1857–1938). Blake was a pupil of François Magendie and a pioneer biochemorphologist. Buchheim established the first teaching laboratory for pharmacology. Abel was a leading American teacher of pharmacology, whose work stimulated the isolation of several biologically active chemicals from crude mammalian glands of internal secretion.

mechanism of particular drug action. This was skillfully probed by Claude Bernard. For many years his correct explanation of the mechanism of action of carbon monoxide on red-blooded animals (in making an irreversible combination with hemoglobin, so that hemoglobin cannot transport oxygen), remained the only successfully solved example in studies of this important scientific question.

At a macromolecular level, drug molecules may act directly with energy exchange, so that if the macromolecules are genes or viruses, mutations may occur. This may be a factor in cancer chemotherapy, whether the mutation be lethal or reversionary to healthy growth. At cellular, tissue, organism, social, or ecological levels of biological organization, introduced chemicals would seem to act chiefly by disturbing some essential aspect of the internal coordinated integration of the system, usually in relation to enzyme patterns, in such a way that the system shows increased or decreased functional activity; decreased activity may result in the disintegration or "death" of the system.

The complexities of mammalian organisms soon made it evident that the mechanism of action of chemicals on living things can more readily be studied on a more uniform population of simpler organisms. The practical importance of antiseptics, which were first tested on bacterial cultures during the latter part of the 19th century, stimulated this development. It has now been extended to tissue culture, with records made by time-lapse movies of the activities of the cells growing in culture under the influence of various introduced chemicals; phase-contrast microscopy is used so that no dyes or other extraneous material need be introduced. Studies of this sort can indeed be quantitated, as my former colleague Charles Pomerat has demonstrated so clearly. It is surprising that the possibilities of using simple plants as pharmacological test objects were so long in being appreciated.

Biochemorphology

The possible relationship between chemical constitution and biological action was first explored by another pupil of Magendie, James Blake (1815–93), that remarkable British nonconformist and pupil of Sharpey and Faraday who became a California pioneer. As a senior medical student, in 1839 he had already shown that drugs act in the mammalian body only after reaching the responsive tissue, and not indirectly by reflex nervous mechanisms. This was part of the problem of considering the absorption and distribution of drugs, and the rates at which these processes may proceed.

In 1841 Blake bravely announced his faith that there must be a relationship between chemical constitution and biological action, and he began to study the relationship by the use of inorganic salts, whose physical-chemical characteristics and structure were much better known than were those of the recently isolated alkaloids. Gross though his studies were, Blake concluded by 1846 that the characteristic pharmacological effect of an inorganic salt is due more to its electropositive ion than to its electronegative one; that there is a relation between the isomorphous properties of elements and the biological action of their compounds; and that with increase of atomic weight in isomorphous groups of elements there is an increase in the intensity of action of corresponding salts. Thus Blake was able to arrange the elements into groups on the basis of the biological effects of their salts. These groups roughly correspond to those of the periodic table, as developed later by the great Russian chemist D. Mendeljeff, although Blake disclaimed any anticipation. Subsequently in California, Blake offered evidence to indicate that molecular vibration rates, which may be correlated with absorption bands in spectrum analysis, may influence the biological activity of inorganic compounds.

Blake's fundamental approach to the relation between chemical constitution and pharmacological action was extended to organic compounds by A. C. Brown (1839–1923) and T. R. Fraser (1841–1920), who showed that various alkaloids with tertiary nitrogen and differing biological actions uniformly acquire a curare-like action through conversion to quaternary ammonium bases. In structure-action relations of organic compounds, some generalizations developed from the studies of B. W. Richardson (1828–96), P. Ehrlich (1854–1915), A. R. Cushny (1866–1926), A. S. Loevenhart (1878–1929), E. Fourneau (1872–1949), and S. Fränkel (1868–1939).

As part of this general problem of biochemorphology, the relation of the physical properties of such substances to their biological effects is also to be considered, as emphasized by Jacques Loeb (1859–1924). Current interest in biochemorphology is greatly stimulated by the discovery of ways and means of reducing the toxicity of existing compounds (as by acetylation of polar radicles) while, at the same time, more sharply developing desired biological effects. These studies have been greatly accelerated by current interest in antibiotics, "tranquilizers," and steroid compounds. F. Schueler is proposing generalized approaches to these matters in his consideration of chemobiodynamics and drug design.

Theoretical Pitfalls in Pharmacology

The first exclusive pharmacological laboratory was operated in the basement of his home in Dorpat, Estonia, by R. Buchheim (1820–79), who also set the conventional tone of pharmacology texts in his 1856 *Lehrbuch*, based on mammalian organ systems. He defined the task of pharmacology as that of first determining at which point in the body a drug may act and then explaining the response on the basis of physical-chemical reactions between the cell constituents and the drug. Since then, many theories of drug action have been proposed without, however, any satisfactory agreement. Thus, there are many different theories of anesthesia, none of which seem adequate to explain the similar effects resulting from so many different kinds of chemical compounds, even including xenon, the chemically inert element. The most refined concepts of physical chemistry may enter into these theories, as is the case with the recent "molecular theory of general anesthesia," proposed by Linus Pauling, in which the anesthetic state is attributed to the formation in the brain of minute hydrate crystals of the clathrate type.

Pharmacology remains chiefly a descriptive science. It is largely a matter of accurate observation and ingenious experimentation, with an analysis of the actions of chemicals on living material in whatever terms are appropriate in current physics, chemistry, and physiology. This follows the procedures established by Buchheim, Schmiedeberg, Fraser, Karl Binz (1832–1913), H. C. Wood (1841–1920), A. Hefter (1859–1925), and John J. Abel (1857–1938) (*1*). The thorough survey of general

pharmacology made so carefully by A. J. Clark indicates the magnitude of the inherent difficulties in pharmacology, which have permitted little more than observational empiricism.

Unfortunately, pharmacology has been so traditionally allied to drug therapy that many fallacious ideas were sure to arise. These, however, are being corrected by statistical methods and "double blind" studies, through new recognition of the ancient principle of the healing power of nature itself and of the faulty reasoning embodied in the phrase *"post hoc ergo propter hoc."*

Again, quite apart from false analogies from drug therapy, there may be errors in interpreting the actions of chemicals in contact with living material on the basis of reactions that may occur in the test tube. When chloral hydrate was first introduced as a depressant drug, it was supposed to exert its narcotic effect by slowly liberating chloroform. Von Mering showed that it is reduced in the body to trichloroethanol, which conjugates with glycuronic acid and is excreted in the urine. The enzymatic mechanisms of these kinds of changes are now being studied.

Pharmacologists remember Ehrlich's disregard of the lack of correlation between in vitro and in vivo effects of drugs: he tried dihydroxyamino arsenobenzene in trypanosome-infected rats and found that it clears the organisms from the blood of the rats, although he knew that it does not kill the trypanosomes in vitro. It was this which suggested to him, with equal lack of direct evidence, that "Salvarsan," the famed "606," might be useful in syphilis, a disease caused by organisms which are only somewhat related to trypanosomes. With something of this same background in mind, my colleagues and I introduced the organic arsenical carbarsone for the effective treatment of amebiasis.

In spite of the rather careful delimiting of the particular scientific problems which differentiate pharmacology from other sciences, it has no characteristic methodology. The isolated perfused mammalian organ technique, used often for bioassay, is essentially a physiological method. Pharmacology is highly empirical and eclectic, using current techniques of biophysics, biochemistry, physiology, and cytology. Much of current interest in molecular biology, so dramatically evolved in genetics, now includes various aspects of pharmacology.

Contrary to frequent sensational news stories, drugs perform no miracles. Drugs can only make living material do more or less what that living material is already capable of doing. The environment of living material can be altered by taking essential chemical factors away from it or by adding abnormal chemical factors to it. Under these circumstances, there may be either increased activity on the part of the living material or decreased activity of the living material, which may go as far as its death.

Significance of Biological Organization Levels

Here it may be appropriate to pause for a moment to consider the significance of a couple of events in that remarkable year of 1847. About the time that Marx and Engels issued their manifesto to the effect that history and economics are explainable in materialistic terms, three young German physiologists, Carl Ludwig (1816–95), Emil Du Bois-Reymond (1818–96), and Hermann von Helmholtz (1821–94) issued a manifesto to the effect that all living processes, including consciousness, are explainable in terms of physics and chemistry. Much evidence has gradually accumulated meanwhile to justify this faith, but another factor, peculiar to living material, raises difficulties.

This factor, the organizational level of living material, was also recognized in 1847, by Rudolf Virchow (1821–1902), who sensed the scope of pathology, the science of disease, as involving deviation in form and function from the norm at cellular, tissue, organism, and social levels of living organization, and founded a great periodical to further this concept. Since then it has slowly been recognized that the characteristics of living material at different organizational levels may vary greatly, so that extrapolation of findings from one level of biological organization to another is precarious.

Meanwhile, we have extended Virchow's concept of organizational levels of biological material at both ends. Life begins with complex macromolecules, such as genes and viruses, and here the principles of physics and chemistry directly apply. Macromolecules may be organized and integrated with many other chemical materials to form cells, which at Virchow's time were thought to be the basic units of life. Cells, however, may be organized into tissues or organs, with specific integrations serving their specific functions. These tissues and organs may further be integrated into organisms, constituting individuals such as human beings. Human beings, and indeed many other organisms, are capable of further integration and organization into societies. These societies in turn may be integrated with a more or less limited ecological environment.

The gamut of biological organization thus runs from macromolecules to ecological milieus. The relatively unknown factor in these various organizational levels is the complex mechanism of integration. Of this we are only currently beginning to get a glimpse, largely by analogy with the techniques developed in cybernetics. Certain it is that chemical agents may produce wholly different results at different organizational levels of biological material. It is clear, for instance, that for amphetamine the effective and lethal dose ranges are quantitatively different at individual and social levels of biological organization. This situation probably exists for many drugs.

Applications of Pharmacological Knowledge

Pharmacology is a rapidly growing science, related to many other biological sciences. Currently, pharmacological studies are adding much excitement to our exploration of the ways in which our brains work. The new field of neuro- and psychopharmacology has blossomed richly as a result of general public acceptance of experimentation on brain activity.

Pharmacology has ties with biophysics, biochemistry, all aspects of physiology, pathology, psychology, and sociology. Like any other biological science, pharmacology is basically dependent upon advances in mathematics, physics, and chemistry.

Pharmacology has direct application in many aspects of professional and vocational endeavor. Its most obvious applications are in the health professions. Historically, pharmacology has long been associated with the medical profession. The obvious applications of pharmacological knowledge occur in the use of drugs to aid (i) in the diagnosis of disease, as in the use of chemicals in functional tests; (ii) in the prevention of disease, as with antiseptics or vitamins; (iii) in the "cure" of disease, as in the removal of infecting parasites by

the chemotherapy of antibiotics; (iv) in the alleviation of the symptoms of disease; and (v) in the promotion of optimum health. The greatest number of drugs are used by physicians for the alleviation of the symptoms of disease.

Similarly, many applications of pharmacology are made in dentistry. Notably, here the local anesthetics are most widely employed. Many drugs of antiseptic action are also used in dentistry, as well as various drugs that have a metabolic effect with respect to the teeth. The current furor over fluoridation of drinking water to prevent dental caries is essentially a pharmacological problem.

Pharmacology may be considered to be the basis for the art of pharmacy. After the biological action of the chemical has been established and some indication has been found for its use, it is up to pharmacists to prepare the chemical in an appropriate way for administration. This is a great and ancient art. It involves considerations of absorption, distribution, and removal of the drug from the body. Many brilliant new advances have been made, particularly in prolongation of absorption, prolongation of action, and promotion of palatability or ease of administration of drugs.

Pharmacology is a necessary part of the nursing profession. All nurses must have information regarding untoward or toxic action of drugs, so as to be able to inform the attending physicians whether or not anything is going wrong in drug medication. Nurses are usually responsible for the administration of drugs in hospitals and should, therefore, have clear knowledge of precise measurement and details of drug administration.

Pharmacology is widely applied in public health, particularly in the control of drinking water and in the mass use of disinfectants for control of infectious disease. The wide use of chemicals in all phases of industry makes it necessary for physicians and public health workers to know a great deal about the toxicity of all kinds of chemicals that may never be developed for specific medical use. It is necessary that this information on toxicity be obtained about all new chemicals in order to protect workers against the dangers of such chemicals if they are used industrially, and to treat such workers, or consumers, if toxic reactions occur.

A broad field for application of pharmacology is maintained in veterinary medicine. This involves not only the control of various diseases in domesticated animals and poultry but also such matters as increasing the rate of growth, modifying sexual development, and even controlling fertility.

Pharmacology is being increasingly applied in agriculture, agronomy, and forestry. Chemicals are being promoted for control of plant growth, whether for pest control or for direct nutrition. Some chemicals so accelerate the rate of growth of plants that they die, and thus these chemicals can be used to eradicate weeds. On the other hand, rate of growth of plants can be increased in such a way as to speed up the use of those plants as food.

By far the greatest use of chemicals in relation to agriculture is in pest control. Often this is directed toward prevention of disease in domesticated animals and humans. There are many effective insecticides as well as rodenticides. Nevertheless, their use always constitutes potential danger to humans as a result of accidental ingestion. Furthermore, the disturbance of the ecological balance in an area by destruction of insects or rodents may have wide-reaching results that are neither anticipated nor desired. Insect and rodent control by means of chemical agents requires great judgment if it is to be satisfactory and free from danger.

The use of chemical warfare agents of various sorts may be considered to be one form of pest control. Again, their use, as in the case of nuclear energy, is fraught with unexpected and often undesired complications and effects. It is unfortunate that general public ignorance of chemical warfare agents, or indeed of the facts on nuclear energy, causes intensive fear and thus lays the basis for mass hysteria.

Chemical warfare not only involves the use of tear gases, irritating vapors, or toxic skin-absorbable poisons, such as were used in World War I, but now includes the possibility of employing highly poisonous "nerve gases" which could be used on civilian populations as well as troops. These "nerve gases" are related to some of the insect toxins, which block the action of acetylcholine esterase, so that symptoms of accumulation of acetylcholine occur. These symptoms may be relieved by high doses of atropine. The extension of chemical warfare agents can go as far as the proposal that volatile tranquilizers be used to take the fight out of large masses of enemy troops or indeed of enemy people.

The applications of pharmacology to sociology are becoming very broad. Here are raised questions as to the ethical use of drugs under various circumstances: Are pain-relieving drugs justified in euthanasia? What is the best way to handle the social aspects of drug addiction? How about the use of drugs for criminal purposes? How far should governments wisely go in controlling the use of drugs, either on an individual basis or under the direction of physicians?

Perhaps the most important application of pharmacological knowledge to social levels of biological organization is that of fertility control. This is particularly important in human societies. Several steroid compounds have now been devised which can control ovulation in women, and it is likely that other chemical compounds may be developed which can control spermatogenesis in men. It is interesting that the steroid compounds controlling ovulation in women can be used both for the purpose of promoting satisfactory ovulation and for the purpose of suppressing it entirely. It now remains to develop these drugs economically in such a way that they may be used on national levels to keep population growth within reasonable bounds, not only for available food supplies but also for satisfying adjustment to land areas.

It has been the very success of applications of scientific knowledge in the control and prevention of disease which has resulted in the current terrifying human population growth all over the world. Also, in association with highly successful applications of scientific knowledge to industry and commerce and with promotion of comfort, convenience, and cleanliness in living, several unexpected and serious difficulties arise, such as extensive pollution of airs and waters, with resulting dangers to human life and welfare. Much of this pollution involves chemicals which may have harmful effects on living material, including humans. These products and effects involve various aspects of toxicology, whether they range from nuclear wastes to combustion fumes or exhausts, or from virus to detergent contamination of drinking and industrial water.

Another serious aspect of our overpopulation problem is the ever-increasing number of old people who are unprepared psychologically, economically, politically, or socially to take care of themselves. Further, there has been no fully satisfactory social means of taking care of them, either. To the often pathetic question of whether or not chem-

icals can maintain youth and bring rejuvenation, the answer so far must be a qualified "no." Chemicals and drugs, however, may help in providing comfort, relaxation, equanimity, and some degree of physical contentment even into advanced old age.

Pharmacology may become increasingly applicable in criminology and in law. This again usually involves some aspect of toxicology, in connection with chemicals or drugs that are used for homicidal or other nefarious or antisocial purposes. By virture of their widespread social use, many drugs, such as alcohol and various addictive drugs, are subject to extensive legal inquiry and well-meaning but often ineffective legal control. Here the psychological aspects of addiction must be better understood by the public generally in order that legal control that will be socially sound and socially effective and acceptable may be provided. Here again, as in many other aspects of the applications of pharmacology and toxicology to human affairs, economic factors intervene and must be considered if satisfactory application of current pharmacological knowledge is to be achieved.

The development of law covering pharmacological and toxicological problems is ancient and significant. The determination of whether or not poisoning has occurred has been a prime legal problem since the Renaissance. Broader aspects of legal control in pharmacology and toxicology concern restrictions on the manufacture, sale, distribution, and adulteration of drugs. It has been proposed that the current problem of "food additives" be handled legally.

While it is not likely that we will be so foolish as to apply pharmacological knowledge to social problems to the extent envisioned by Aldous Huxley in *Brave New World*, the capacity for doing so certainly exists. Fortunately, pharmacological studies on the brain are helping us to understand something of the complex way in which our amazing brains function. This is particularly important to us at this time, when our scientific knowledge of the world about us is increasing so rapidly. This verifiable information about our universe gives us the capacity to control our environment in many surprising ways. Chemicals can play an enormous role in this matter, not only in increasing sources of food for our ballooning populations but also in developing our environments in a manner that may be satisfying for us.

On the other hand, our knowledge of the ways in which our brains function has lagged. It may well be that the pharmacological studies which have resulted in tranquilizers, antidepressant drugs, and psychomimetic compounds are furnishing tools of the utmost importance in the analysis of the complexities of our integrated nervous systems. The more we understand the ways in which our brains work and are conditioned, the better able we may be to understand ourselves and our relation to our environment.

Actually it appears possible that chemicals can be developed which may have an important effect on our individual and thus on our social satisfactions. Pharmacological knowledge is indicating much of significance about the highly complex chemical integration within certain cells of the brain stem where increased activity leads to behavior directed toward self-preservation on the one hand, in the search for food, and to species preservation on the other hand, in the drive for sexual activity. Enhanced activity of these cells seems to be dependent upon the metabolic build-up within them of a considerable complex of many types of chemical agents. When these spill through the cells, depolarization occurs and cellular activity diminishes. This is reflected in the feeling of "satisfaction" which we feel as individuals when we ingest food or when a sexual orgasm occurs. Some tranquilizers, such as reserpine from the anciently used serpent root of India, can bring some of these chemicals, such as 5-hydroxytryptamine, out of the cells, thus depolarizing them and reducing their activity.

It remains for us, as our experience and wisdom and scientific information increase, to apply to ourselves, and thus collectively to the societies in which we live, the knowledge that may help us to adjust more satisfactorily to each other and to our environment. There are thus interesting philosophical overtones to pharmacological study, and they bring in many aspects of the ancient Greek concepts of logics, ethics, and esthetics.

Economic Aspects of Pharmacology

The applications of pharmacology in the health professions and in agriculture have been greatly stimulating to industry and have resulted in a phenomenal growth of drug manufacturing. This in turn has resulted in commercial influences of all sorts in stimulating increased pharmacological research, with further applications toward hoped-for benefits in practical affairs and profit. The remarkable possibilities for chemical manufacture inherent in the close relationships between chemicals used as drugs and those used as explosives or for other industrial purposes was apparent to the highly developed German industry before World War I. Many of the unfortunate characteristics of that development still exist.

There is great interest in our own country in some sort of control over excesses in the food and drug industry. The food and drug industry would be wise to regulate itself in a satisfactory way, so that governmental control would not be necessary. We have altogether too much bureaucracy as it is, and if we are to preserve our standards of individual freedom and responsibility in our social unity, we must do all we can to reduce government control and regulation. Admittedly this is difficult.

The German pharmaceutical industry before World War I learned to take advantage of patent and copyright laws. In most countries patent rights to a product run for a definite number of years, 17 in the case of the United States; on the other hand, copyrights may run indefinitely. This is the case with trade names. The German drug manufacturers learned early to advertise trade names for drugs, so that when patent rights expired and the product came into open competition, physicians would continue to call for the drug under its trade name, because this would be the name they would most easily remember.

As it is, most drug manufacturers now have trade names for the drugs they sell. In addition, there is usually some sort of public name, which represents a generally agreed upon word symbol usually designating some aspect of the chemical make-up of the new drug. The trade name, however, is quite commonly selected from the standpoint of suggesting the use of the drug.

There is great confusion regarding drug names. Some recently introduced drugs may have as many as three or four trade names, as a result of licensing. It would seem that this confusion over names could readily be avoided by general use of the public name for a drug (I have a personal antipathy toward the term *generic name*; this term is a misnomer). Public names could be used with the designation of the company that manufactures the drug after

the public name, so as to identify the product as coming from that manufacturing company. This would certainly guarantee the quality of the product and would help to advertise the position and distinction of the drug manufacturing company. It would seem that drug manufacturers could unite in developing this principle in the use of public names for drugs so as to reduce the appalling confusion now existing in this matter.

When I appeared before the Kefauver Committee in regard to the control of alleged abuses in drug manufacturing and advertising, I recommended that patents on drugs be extended to 25 years, so that the manufacturers could be sure to get a reasonable return on the heavy investments they make on their research and development programs. On the other hand, I proposed that if this were to be the case, then any trademark that might be granted in connection with a new drug be cancelled when the patents expire. I don't know whether this would help or not. There certainly was little interest in the idea!

I have been amused at the specious claims of drug manufacturers with regard to the significance of trade names for drugs as a guarantee of quality. It would seem to me that the public name of the drug, followed by the name of the company which manufacturers it, would give equal assurance of quality.

It does not seem in the public interest to have a lot of unnecessary minor modifications of well-known drugs, all of which have the same general actions, in order to achieve some economic advantage as a result of clever advertising. Nevertheless, this is constantly done. In an authoritarian state, such as Russia, this matter may be handled simply through the authority of some agency in selecting the best drugs available for particular purposes and allowing only those to be manufactured and made available. On the other hand, in Japan any drug, except for certain addictive ones, is readily available for open purchase in drug stores, even including vaccines and antisera for self-immunization. The people of Japan, however, are amazingly sophisticated in regard to matters of health, and the drugs available to them are carefully packaged with full pharmacological information included.

Our economic policies in relation to pharmacology often are in conflict with scientific ideals and tradition. Consider the advertising used with conventional hypocrisy by drug manufacturers in promoting the sale of their special products: in some cases, as in TV commercials on aspirin preparations, it is intellectually disgusting; in others, as in professional journals directed to members of the health professions, it is intellectually insulting. Usually it is not informative but is slickly persuasive, as if physicians were status-seeking housewives.

The economic aspects of pharmacology involve political considerations insofar as legal regulation is concerned. These matters can become extremely confusing and often seem to be tempests in teapots. Many fundamental principles are involved, however, and the economic aspects of pharmacology continually have to be reviewed, particularly by those who are in the actual business of devising and developing new drugs for a particular purpose.

In Prospect

Pharmacology is a broad scientific discipline, closely correlated with all other areas of scientific interest, from astronomy to zoology. It is becoming increasingly dependent upon mathematics, physics, and chemistry, and it is increasingly related to the character of the organizational levels of the biological material with which it deals.

The fundamental scientific problems which differentiate pharmacology from any other scientific discipline are concerned with the interrelations of chemical agents and living material from the standpoint of dosage of the chemical in relation to the effects produced on the biological material; the absorption, distribution, metabolism, and removal of chemicals from living material; the localization of the point of interaction between chemicals and living material; the ways in which chemicals can act upon living material; and the relationships between the physical constitution of chemical compounds and their biological actions. These basic problems of pharmacology were well outlined by the middle of the 19th century, largely under the influence of the great French biological scientist François Magendie.

Pharmacology, however, still remains chiefly an empirical science, in which the analysis of observed phenomena is the basis for study and experimentation. From such analysis it is certain that broad generalizations may emerge which may have significant consequences for related scientific disciplines, particularly biophysics, biochemistry, physiology, histochemistry, pathology, psychology, and by extension, sociology. Pharmacological knowledge is being increasingly applied not only in the health professions but also in agriculture, industry, law, and politics. The applications of pharmacology to practical human affairs frequently result in unforeseen consequences which require careful study and judgment if they are not to prove harmful in the long run to human beings and ecological environments.

Pharmacological knowledge has vastly increased during the past century. It has produced many important chemicals, which have aided materially in the control of disease and in the promotion of optimum health and good living. The increasing applications of pharmacological science may provide increasing advances in long-range human welfare. However, as in the case of other sciences, pharmacology must be well balanced by humanistic considerations: the humanities and the arts give training in judgment, in propriety, and in the fitness of things which are essential for the wise application of scientific knowledge for human benefit.

Pharmacology shares with all the other sciences responsibility for getting at the verifiable truth about ourselves and our environment. Pharmacologists share with all other scientists the responsibility for judging wisely to assure the least possible disturbance of the natural balance of our world, which has taken so many millions of years to evolve. Pharmacology as a science can aid us through its applications, if they are wisely made, to obtain those satisfactions in living which we all crave—satisfactions the drive for which is an inherent part of the built-in make-up of our integrating neurohumoral mechanisms for self-preservation and for the preservation of our human species, with its presumed humanity.

Note

1. In the 114 years of AAAS history, a pharmacologist has held the presidency only once before. This was the revered John Jacob Abel (1877–1938), long professor of pharmacology at Johns Hopkins University, Baltimore. He presided at the June 1932 meeting in Syracuse and at the December 1932 session in Atlantic City. As retiring president he addressed the December 1933 meeting in Boston on "Poisons and disease," in a review of his studies on tetanus toxin.

Science and Human Survival

Unlimited war is self-defeating and an alternative must be found by a new science of human survival.

War is today a social problem of catastrophic force and overshadowing urgency. The basis of war is power, and power is a product of science. Science is therefore deeply involved in this problem, and scientists have a particular duty toward its solution. For the establishment of national policy on war —or peace—the public needs to learn the relevant facts and discuss their meaning. We believe that it is the obligation of scientists to make these facts known, to estimate the consequences of alternative policies, and, if need be, to seek new solutions (*1*).

War is a form of social action that is intended to conserve and protect the social order, or to extend it. It is one response to a basic social need for protection. Despite its inhumanity and wastefulness many societies have thus far been able to adapt to the increasingly stressful effects of war and to survive its growing violence. However, current war preparations involve new weapons —nuclear, chemical, and biological— that have not had a substantial trial in actual combat. There is therefore no historical evidence that adaptation and survival are possible in this type of warfare, or that these untried weapons can achieve the purpose for which they have been developed—the protection of nations or social orders.

Growing Destructive Power of War

The destructive power of modern weapons is increasing geometrically. The first nuclear bombs exploded in 1945 released energy equivalent to about 20 kilotons of TNT; in the test explosions of 1948 the maximum size was about 50 kilotons; by 1953 explosions of the order of 1000 to 10,000 kilotons had been achieved, and this year 30,000- and 50,000-kiloton bombs were exploded. In the 16 years since the first nuclear explosions the size of available weapons has about doubled every year.

The present arms race is the outcome of the widespread basic knowledge of nuclear forces, the essentially unlimited power of the resultant weapons, and the existence of several nations capable of building them. Because some of these nations regard each other as potential enemies, a rapidly accelerating process of competitive armaments has taken place. One nation arms to deter a possible attack from the other; fearing that these arms may be for aggression rather than defense, the second nation responds by an even greater armament; and the process continues. Defensive measures such as shelters follow the same pattern, for they too will tend to elicit a more powerful offense. The arms race is a typical self-accelerating process, and the destructive power of modern weapons is growing at a rate which becomes faster each year.

Modern technology is not only powerful but also complex and fast-acting. The development of rocket missiles has reduced the time for delivery of a nuclear weapon to about 20 to 30 minutes. In that brief time the target nation must discover that the attack has been launched, work out the missile's course, determine its national origin, decide on an appropriate response, and set in motion its own defensive and offensive measures. To achieve the necessary speed there have been developed elaborate networks of detectors, communication lines, and electronic computers. Modern systems of warfare have become so complex and swift that they can no longer be controlled consistently by human judgment alone.

Because of the complexity of modern war systems, considerable attention has been given to the problem of accidental war. Part of the elaborate instrumentation is designed to set up multiple controls and other devices to prevent mechanical or personal accidents, and, according to some observers, reduces the probability of an accidental war. However, Norbert Wiener has suggested that complex computer systems may sometimes respond to a situation in a way that is not anticipated by their human controllers, and do so at such speed as to produce a wrong decision before there is time for correction. He believes, for example, that a machine designed to solve war problems might sometimes operate in an unexpected way and "win the war" at a price that nobody wants to pay (*2*).

Regardless of which view of the effect of instrumentation on the probability of accidental or unwanted war one accepts, it is clear that the hazard is a real one. The Mershon report, which has surveyed the problem, concludes, "Taking together all the dangers, there is a significant chance that a major accidental war may occur sometime in the 60's" (*3*).

Immediate Effects of a Nuclear War

The immediate destruction expected from a full-scale nuclear war has been the subject of fairly detailed study, at least in the United States, and certain estimates are possible. The Joint Congressional Committee on Atomic Energy and the agencies cooperating with it have performed a valuable service in summarizing the relevant evidence on the effects of nuclear war (*4, 5*). These depend, of course, on what assumptions are made about the nature of an attack. In the congressional hearings, and in most subsequent discussions, it is assumed that the United States is attacked with 1- to 10-megaton weapons, totaling about 1500 to 3000 megatons, and that no adequate shelters have been provided. In these circumstances it is estimated that the attack would leave some 40 to 70 million dead within a few weeks; a lesser number would be injured and survive, depending on what medical facilities withstand the attack. According to a recent analysis of the effects of 20 megatons of nuclear explosive on the New York metropolitan area, total casualties of about 60 percent of that population would occur (*6*).

Any city struck in such an attack would be demolished by blast and fire storms. It is generally concluded that a massive nuclear attack on the United States could destroy most of the nation's major cities.

It is one of the tasks of the AAAS Committee on Science in the Promotion of Human Welfare to encourage discussion of scientists' obligations toward questions of public policy that arise from the social effects of scientific progress. In keeping with this responsibility, some of the members of the committee recently held a conference to discuss the relationship between science and modern war. This article summarizes the views developed by the conference and is published to stimulate further discussion. Those participating were Barry Commoner, Washington University; T. C. Byerly, Agricultural Research Service, U.S. Department of Agriculture; Lawrence K. Frank, Belmont, Massachusetts; H. J. Geiger, School of Public Health, Harvard University; Margaret Mead, American Museum of Natural History; and Frank W. Notestein, Population Council, Inc.

. This scale of killing and destruction is so enormous that certain broad generalizations regarding its social consequences can be made. At the very least, all social and economic processes which depend on large cities would be massively disrupted: communications, transportation, finance, a considerable part of light and heavy manufacturing, major medical facilities, institutions of higher education, scientific laboratories, libraries, centers of government. If we add to this the widespread effects of fires and radiation outside the range of direct hits, it becomes apparent that such an attack would largely destroy our present social structure. Whatever operations were possible immediately after the attack would necessarily require a system of economic, social, and political organization radically different from that which we now enjoy.

In general, the development of a shelter program cannot greatly influence the conclusion that a massive nuclear attack would have the immediate effect of destroying the social structure. A particular shelter system is designed to resist a certain assumed intensity of attack, and its success depends on the validity of this assumption. But an opponent can be expected to respond to such a defensive move by stepping up the intensity of attack. Any shelter system short of one that places the nation's entire population and industry permanently underground can be negated by a corresponding increase in the attacker's power. In fact, as Brown and Real (*7*) have pointed out, the mere preparation to resist an increasingly massive nuclear attack—that is, the deeper and deeper emplacement of more and more of our activities into underground shelters—would, even in the absence of nuclear war, make profound changes in our normal social structure.

There is, we believe, no escape from these conclusions about the *immediate* effects of a full-scale nuclear war on the belligerents: it would kill a considerable portion of their populations, destroy the major cities, and disrupt the present structures of the societies which it would be intended to protect.

Long-Term Effects of Nuclear War

The long-range problem is vastly more complex than the immediate one. It presents the following general questions: (i) What lasting effects would the great fires and radioactivity produced by the attack have on the biological system (soil, water, air, plants, and animals) on which man depends? (ii) How would the increased death rate, widespread disease, and genetic effects of the war affect the vitality and viability of the survivors? (iii) Would the immediate destructive effects of a nuclear war cause major irreversible changes in the economic, social, and political organization of our society? (iv) How would the foregoing effects—and the aftermath of direct experience with the nuclear attack—influence the behavior of human beings, and how would new patterns of behavior influence social organizations and operations?

The scientific evidence that can be marshaled to answer this formidable array of questions, which is summarized in congressional hearings held in 1959 (*4*) and 1961 (*5*), is very limited and uncertain. The problems are listed above in increasing order of complexity. The simplest, though still exceedingly difficult, problem is the ecological outcome of a nuclear war. A discussion of this problem by an ecologist, John N. Wolfe (chief of the Environmental Sciences Branch, Division of Biology and Medicine, Atomic Energy Commission), begins with this statement: "The long-time ecological effects of nuclear war are nearly impossible to assess and even difficult to speculate about" (*4*, p. 840). In his opinion, ecological recovery—for example, reestablishment of the continent's plant life—would require many decades, but more optimistic opinions have been expressed by others (*5*).

The more complex problems associated with recovery of the economic and social structures following their disruption in a nuclear attack were considered at the congressional hearings of 1961 (*5*). Discussion by Sidney G. Winter, Jr., of the Rand Corporation, of the economic recovery problem concluded that sufficient industrial capacity would probably remain after a nuclear attack to support eventual economic recovery; but on questioning it developed that this estimate was based on the assumption that transportation would be unharmed in the attack (*5*, p. 327). The conclusion that economic recovery is feasible was further qualified by the statement that it does not apply "to possible future situations when extensive blast shelters might be available" (*5*, p. 326). According to this testimony, in a nuclear war that would destroy a given proportion of the nation's industrial capacity, economic recovery would be possible so long as the loss of life in the initial attack would be correspondingly large (*5*, p. 315). If the ratio of survivors to remaining industrial capacity were to become too great, the resulting demand on the limited goods available would be overwhelming and cause a general failure in social organization (*5*, p. 313). Thus, what is proposed to enhance *immediate* survival of the population (shelters) has a contradictory effect on the balance between post-attack industry and population that is deemed necessary for *long-term* survival. In a piecemeal treatment of recovery from nuclear war, separate problems appear to be soluble just because they are artificially isolated from the web of interconnections that distinguishes the complexity—and the actuality—of society, an illusion that is dispelled when the fragment is restored to its proper place in the whole.

If we take the evidence presented at the recent hearings as a summary of the present state of knowledge, and consider in its entirety the problem of recovery from nuclear war, there is, we believe, no scientific basis at present for

a useful prediction of what kind of society—if any—would emerge from the ruins.

It will be argued that such fears and uncertainties have always accompanied the development of new forms of power, that these hazards have always been overcome, and that the new forces have been successfully put to good use. We will be reminded that the invention of dynamite was supposed to render war inadmissibly fearful, but that society learned to accommodate itself to this new destructive force. In reply we would point out that social adaptation to new forms of destruction has always, in the past, been achieved by actual experience. Society has "learned to live" with the new inventions by a series of historical experiments, rather than by predictive analysis. What is at issue today is whether or not we can afford to take the appalling risk of attempting to learn from experience whether society—and indeed human life—can survive a nuclear catastrophe.

We are obliged to reassert that the analytical powers of science, which have until now helped to guide society toward its present levels of accomplishment, fail to predict whether human societies would ever return to their present state of competence following a nuclear war. If society embarks on the path of nuclear war, science cannot now offer enlightenment on the end result.

Even if by some unforeseen development we could tomorrow discover how to survive a nuclear war, the basic problem will remain, for other kinds of equally devastating wars are also possible. Shelters that might protect from the blast, fire, and radiation of nuclear war could yet remain vulnerable to an attack with chemical agents. If a way were found for defense against a chemical assault, farmlands would remain unshielded from fertility-destroying agents. Science has now achieved such mastery of nature as to place in human hands the power to end human life. This basic scientific knowledge is widespread, and will grow as science makes further advances. Although stockpiled bombs can be destroyed, the knowledge of how to make new ones cannot be obliterated from men's minds. From now on, mankind must live in a world in which a suicidal war—by whatever means—is always possible. Our problem is not the prevention of a particular war but the continuous protection of human society from a potential danger that will in the foreseeable future continue to threaten the human species with extinction.

We have examined the effects of modern war with respect to our own society. However, we believe that the conclusions apply with equal force to all belligerents in an unlimited war. In view of the world-wide effects of radioactive fallout and of the economic interdependence of the modern world, no nation can hope to escape the catastrophic effects of such a war.

We must conclude that society can no longer be defended by an unlimited war. If we commit the decision of conflicts between opposing societies to such a war, both will be largely destroyed within days and their remnants will face an uncertain future. If we permit such a war to occur in the future course of human history, we run the risk of ending human history altogether.

This is a major transformation in the human condition, and in the nature of human society. Peace, which was until now a human *want*, has become a human *need*. But so long as there is no alternative to war as a means of national security, the need for peace—and for survival—will conflict with the need for social protection. It is this unresolved conflict that has bred the crisis of our time.

The Responsibilities of Science

We believe that science has a commanding responsibility to help mankind survive. Whether society shall continue to rely on war—which is now so dangerously unfit for its protective function—is a social decision in which scientists have no greater or lesser rights and duties than other citizens. But, in the discussions which must precede this decision, and in the development of the means for putting it into effect, science has a special duty and an historic opportunity.

If this crisis is to be resolved by rational social action, the public must become aware of it, understand its dimensions, and appraise the possible solutions. For all these purposes, the public must have the relevant technical facts. Scientists, who are the custodians of this information, must be prepared to bring it before the public.

To accomplish this educational task, scientists will need to overcome certain difficulties. One problem is to remove the obstacles which now tend to obstruct the flow of technical information to the scientific community. Much of the information about war is not easily accessible to scientists, for it often appears in special reports which rarely find their way into the scientists' libraries. This information must be brought more fully into the stream of ordinary scientific communication if scientists are to be adequately prepared for public education on these problems.

Another difficulty is caused by the political tension that is naturally associated with the problems of war and peace. Any scientific finding about these issues is almost certain to be construed as supporting some political beliefs and contradicting others, and there may be a tendency toward social pressure against the scientist who attempts to disseminate it. Such constraint on the free and independent scientific examination of these problems is an obstacle to understanding and a hazard to the rational development of social decisions. If scientists have the obligation to inform their fellow citizens about grave issues, citizens have a reciprocal duty to defend the scientists' right to be heard without prejudice.

By providing the public with the necessary facts—objectively and calmly—scientists can help overcome the uncertainty, confusion, and fear that have been generated by the war crisis.

Science must also assume a new obligation in the present crisis. Science has traditionally served all human needs, among them the need for protection against threatened or perceived harm. The same duty that has placed science at the command of warfare now requires that scientists should with equal devotion serve the social need for peace and find a means of protecting society that does not run the risk of destroying it. This is a great historic challenge, and we believe that science is ready to accept it.

To provide time to devise an acceptable alternative to war, negotiations to limit armaments and recourse to war are urgently needed, and scientists are already performing valuable services in facilitating them. Scientists have done a great deal—but can do considerably more—to help disseminate and apply technical information for the promotion of human welfare in all the nations of the world. If every nation becomes capable of protecting its own people against hunger and disease, political conflicts that might set off an unlimited war can be reduced. But these measures will not alone solve the basic crisis of

war, for peace is a process, not a state of truce. What are lacking to establish this process are instrumentalities for the maintenance of peace and for the self-protection of society that are free of the self-defeating faults of modern war.

The importance of peaceful means of resolving social conflict has, of course, long been recognized. Students of human behavior and of social, economic, political, international, and legal processes and many research organizations and foundations have made important contributions to the understanding of social conflicts and have investigated possible methods of resolving them. But these efforts, valuable as they are, do not measure up to the urgency of the need.

Separate analyses of the different aspects of the problem of peaceful resolution of national conflicts are inadequate to the task. These problems are inherently complex, and a scientific attack on them, if it is to succeed, must acknowledge and deal with this complexity (*8*). For example, the negotiations on a nuclear test ban treaty—such a treaty represents only a rather small part of the total problem—involve a wide array of questions in the natural sciences, sociology, and economics.

We believe that if the complexity of the problem is not only recognized but accepted in advance as inescapable, it can be solved. For this purpose we will need to marshal the full resources of *all* the sciences. We shall need to use the special experimental skills of the natural sciences and the knowledge of man accumulated by the social sciences of anthropology, human biology, psychology, sociology, political science, economics, and history. We can no longer risk actual historical experiments to prove out the alternative methods of survival open to the human race. But with creative scientific imagination we can develop ways to simulate the problems in the laboratory—for example, through models based on new ideas and approaches—that will enable us to deal with the many-sided problems and to test the suitability of new procedures. In the past, the physical, biological, and social sciences have been separated by their reliance on different approaches. Today, to meet the new needs of the entire human species—which have resulted from the application of science to the protection of individual societies and the resulting obsolescence of warfare—the concepts and methods of all the sciences must be combined. We can then hope to devise new social inventions to protect all mankind from self-destruction.

Are these hopes unreal? Can such a complex scientific assault on so difficult a problem really succeed? No one knows. But we do know that modern science has the facilities, the techniques, and the material strength that can be directed toward this task. As evidence of this capacity we need only cite the current accomplishments of science, and the considerable success of recent interdisciplinary and international scientific projects (the International Geophysical Year, the various United Nations programs, and antarctic exploration).

Despite its formidable complexity and close association with deeply held social ideas, the problem of modern war is of a type that is not wholly new to science. Science has some history of success in dealing with such issues. In a certain sense the present problem resembles the historical crisis due to the impact of Darwinism on Victorian society—or of the Copernican revolution on the medieval views of man and the universe. In these historical trials the views fostered by science finally prevailed. This success reflects the special strengths of science. Science has developed methods for using man's most powerful instrument, reason. Science has learned how to face the actualities of nature, define their limits, analyze and direct them. Science follows rules of procedure which help to assure the validity of its methods: insistence on objective open discussion of results, continuous correction of errors and omissions. Science has taught its practitioners to rely on what we know about nature, rather than on what we wish nature to be. Science has powerful means for correcting faulty human conceptions such as the continuing belief that human societies can be conserved by modern war.

We call for the establishment of a new collaborative science, *the science of human survival*, which will apply the full strength and wisdom of all the sciences to the solution of the crisis created by the obsolescence of war.

We cannot now provide a blueprint of the structure of the new science, nor specifications of all it may accomplish. But some of the problems that it must solve are now known. Given this knowledge, we believe that the new science can develop practical means for the solution of the crisis generated by the suicidal character of modern war.

The present danger of war derives from the powers of science and the decisions of society; and its resolution also depends on these agencies. It lies within the power of science to illuminate the self-destructive nature of modern war and to discover new social inventions to replace it. It is up to the citizens—in this nation and throughout the world—to determine that the powers of science will be used not to wage war but to create the conditions of peace.

The great changes that science has made in the human condition form a procession of present accomplishments that yesterday were only fantasies and dreams. This history gives us hope that science can help mankind realize tomorrow what is today the dream of peace.

References and Notes

1. The basis for this conviction is set forth in the report of the AAAS Committee on Science in the Promotion of Human Welfare, *Science* **132**, 68 (1960).
2. N. Wiener, *ibid.* **131**, 1355 (1960).
3. J. B. Phelps *et al.*, "Accidental war: some dangers in the 1960's" (Mershon National Security Research Program, Ohio State University, Columbus, 1960).
4. "Biological and environmental effects of nuclear war" (Joint Congressional Committee on Atomic Energy, Aug. 1959).
5. "Civil defense—1961," Hearings before a Subcommittee of the Committee on Government Operations, House of Representatives, 87th Congress, 1–19 Aug. 1961.
6. T. Stonier, "The anticipated biological and environmental effects of detonating a 20 megaton weapon on Columbus Circle" (Scientists' Committee for Radiation Information, New York, 1961).
7. H. Brown and J. Real, "Community of fear" (Fund for the Republic, New York, 1961).
8. The importance of dealing with inherent complexity has been pointed out by Warren Weaver in the following statement [*Am. Scientist* **36**, No. 4 (1948)]:

   "These problems—and a wide range of similar problems in the biological, medical, psychological, economic and political sciences—are just too complicated to yield to the old nineteenth-century techniques which were so dramatically successful on two-, three-, or four-variable problems of simplicity. These new problems, moreover, cannot be handled with the statistical techniques so effective in describing average behavior in problems of disorganized complexity.

   "These new problems, and the future of the world depends on many of them, require science to make a third great advance, an advance that must be even greater than the nineteenth-century victory over problems of disorganized complexity. Science must, over the next 30 years, learn to deal with these problems of organized complexity."

   A similar judgment with regard to one discipline has been made by J. David Singer, who notes [*Behavioral Sci.* **6**, No. 4 (1961)]: "The point which needs to be stressed here is that political science in general, and international relations in particular, suffer from a serious paucity of concepts and models by which we might seek to describe, explain or predict with fullness and clarity. Our conceptual poverty strikes this writer as perhaps the greatest single handicap in the development of everything from low-level empirical generalizations to a full-blown theoretical scheme."

Howard Percy Robertson, Physicist

The nation lost a distinguished mathematical physicist, educator, academician, adviser on military affairs, and humanist in the death of Howard P. Robertson on 26 August, following a traffic accident. His friends have lost a companion of unusual intellectual power, breadth of knowledge, courage, and wit, who enriched their lives in every contact with him.

Robertson was born on 27 January, 1903 in Hoquiam, Washington, receiving his education in the schools of that state through the bachelor of science and master of science degrees at the University of Washington, in 1922 and 1924. He completed his graduate studies at the California Institute of Technology, where he was a teaching fellow in mathematical physics. He received the Ph.D. degree there in 1925.

Like many of his generation, Robertson went to Germany for postgraduate study at Göttingen and Munich, on a National Research Fellowship. He returned to the California Institute of Technology as assistant professor and remained from 1927 to 1929. He then moved to Princeton, where he was a member of the faculty for 18 years, rising to the rank of full professor in 1938.

Howard Percy Robertson

In this period of research and teaching, Robertson's interest and work centered in mathematical physics, chiefly differential geometry, cosmology, and the theory of relativity. His first contribution was a new representation of the de Sitter universe, which brought out its physical features more clearly. He turned then to the theory of the expanding universe and made contributions to this theory which are of both mathematical and astronomical interest.

At a memorial service held at the California Institute of Technology on 30 August, Paul Epstein gave the following summary of Robertson's chief contributions to science.

> The scientific personality of H. P. Robertson was characterized by exceptional mathematical powers, coupled with a deep insight into physical processes. His chief interests lay in general relativity, in which field he will be mainly remembered for two contributions of outstanding importance.
>
> (1) Early in his career he gave the solution of Einstein's cosmological equations for the case of a homogeneous and isotropic universe. This solution served ever after as the basis for most of the vast number of papers written by other authors on relativistic cosmology.
>
> (2) By bringing to bear his great mathematical skill on the two-body problem in general relativity he succeeded in obtaining its solution, a task which before him had been unsuccessfully tried by almost all the best specialists.
>
> Of his work on subjects other than relativity, the most important is perhaps that relating to the quantum-dynamical principle of indetermination. Instead of restricting himself to the theory of measurement of a *coordinate* and of the associated *momentum*, Robertson asked about when and to what extent *any* two physical observables whatever can be simultaneously measured, and in a simple and elegant way he set up the conditions for this. In all modern textbooks the principle of indetermination is now presented in this generalized form.

In 1947 Robertson returned to the California Institute of Technology as professor of mathematical physics and, except for certain leaves of absence, served in this position until his death. He was elected a member of the National Academy of Sciences in 1951 and its foreign secretary in 1958. He was also a member of many other scientific societies, including the American Mathematical Society, the American Philosophical Society, the American Astronomical Society, and the Edinburgh Mathematical Society.

World War II brought Robertson from the highly specialized fields of theoretical physics into the circle of those engaged in research on military problems, beginning with service with the National Defense Research Committee from 1940 to 1943 and with its successor agency, the Office of Scientific Research and Development, as scientific liaison officer in London. His scientific interest turned to problems of elasticity, hydrodynamics, and shock wave propagation, much of his work in these areas remaining unpublished.

In 1945 Robertson was chief of the Scientific Intelligence Advisory Section of Supreme Headquarters Allied Expeditionary Force in France, and a scientific adviser to the United States military government in Germany. In the following years he served as scientific director of the Weapons Systems Evaluation Group of the Department of Defense, scientific adviser to General A. M. Gruenther (supreme commander of the Allied Forces in Europe), member of the President's Science Advisory Committee, and chairman of the Defense Science Board.

For his war service he received the U.S. Medal for Merit for "solving complex technical problems in the fields of bomb ballistics, penetrations and patterns and enemy secret weapons."

Robertson was one of those scientists able to make the transition from specialized scientific problems to the broader field of scientific statesman. In a tribute to his work as military adviser, Clark Millikan has emphasized not only this breadth of interest and talent but Robertson's toughness and courage, and his failure to be intimidated by rank or position, qualities which, with his sheer intellectual power, brought widespread respect for his ability and judgment. Millikan states the belief shared by many of Robertson's friends and colleagues that his work saved countless allied lives and shortened the war.

HUGH L. DRYDEN
National Aeronautics and Space Administration, Washington, D.C.

Science and the News

The Constitution and Religion: How High the Wall of Separation?

During the school aid debate last year the Health, Education, and Welfare Department, at Senator Morse's invitation, prepared a legal memorandum on the constitutional problems of aid to church schools; to no one's very great surprise, it found that everything the Administration was proposing seemed to be constitutionally acceptable, but that what the Administration was opposing was, unfortunately, unconstitutional. Specifically, the Department's memorandum suggested that aid for clearly nonsectarian purposes, such as for laboratory equipment, would be all right for religious elementary and secondary schools; that almost any kind of aid *not* specifically for religious purposes would be all right for universities; but that the general-purpose loans that Catholics were asking for parochial-schools would be out of bounds.

Now the Catholic position has been formally stated in a countermemorandum released last week by the National Catholic Welfare Board, and this, equally unsurprisingly, finds that the Welfare Department is mistaken, and that almost any kind of assistance to parochial schools would be constitutional so long as the proportion of aid did not exceed the portion of the school budget fairly chargeable to secular education. Two other major positions have been argued for: one is that any aid to church-related schools, at any level of education, and for any purpose, would be unconstitutional; the other is that federal aid to education in general is unconstitutional. The first of these commands a good deal of popular support, but virtually no support among the leaders of either party; the second is supported only by conservatives of the Goldwater school, but is not taken seriously in other quarters. Neither one, though, stands the remotest chance of ever being accepted by the Supreme Court, even though, in one of the paradoxes with which the law abounds, the first is actually the position that is closest in accord with a straightforward interpretation of the Supreme Court's opinions. Goldwater's position is that Congress has no power to spend money on anything that is not specifically mentioned in the Constitution, a view which was finally and firmly turned down by the Supreme Court in 1936, and which, if taken seriously, would make half of what the government is doing, such as sending a man to the moon, unconstitutional. The no-aid-to-any-church-school view, however, can point for support to the Everson case, the leading decision on aid to church schools: "No tax in any amount, large or small, can be levied," said the Court, "to support any religious activities or institutions, whatever they may be called, or whatever form they may adopt to teach or practice religion." This is pretty strong language, and might seem to put in doubt almost every program on the books giving support to higher education, since under all of them money goes to church-connected colleges. No one is much concerned, though, for if the Court were to take *that* position, nearly everyone would regard it as a disastrous thing to do, which is a nearly absolute guarantee that the court will never do it.

As for the two major positions, the Administration's and the Church's, both took a similar line of reasoning to get around the Court's apparent position: this was generally that a church school could be thought of as having two components, a religious component, for which all aid is prohibited, and a secular component, to which any aid is permitted. The awkward point for the Catholics was that this, pretty clearly, was not what the court had in mind when it wrote its decision; in the case, the court had actually upheld, by a 5 to 4 vote, the constitutionality of a New Jersey law providing free bus transportation for private as well as public school children, but on the grounds that it was only incidentally aid to the schools involved, and mainly a program to get children "regardless of their religion, safely and expeditiously to and from accredited schools." This might be stretched, as the Administration did in its argument, to allow room for quite a bit of aid under a series of narrowly defined specific programs, each of which would be justified on the grounds that it was merely a benefit for all school children, regardless of religious considerations, and not to be ruled unconstitutional merely because it incidentally benefited a religious school. But it was stretching it pretty near the breaking point to argue that it allowed room for across-the-board help, where it became awkward to argue that the help would only incidentally benefit the school.

The awkward point for the Administration was that, having taken the politically necessary position of regarding across-the-board grants or loans as unconstitutional for schools, it had to explain why similar grants or loans would be all right for colleges. What the Administration did was abandon the Everson case and argue that the nation's private institutions of higher education are just too important to deny support to merely because some of them are church-connected. But once this argument is adopted the question becomes one clearly over public policy rather than over what is constitutional. It becomes perfectly legitimate to argue that as a matter of public policy, again, private schools should be given at least the minimum amount of support necessary to permit them to survive, on the grounds that some diversity is good for the country. Once the question comes down to what is wise public policy, the matter is one for Congress rather than the Supreme Court to decide.

In practice, it is at least very likely, that this is the view that will prevail, and that any laws which go through Congress in the coming years relating to support for private education will be accepted by the Supreme Court. But so far as general aid to schools is concerned, the problem at the moment is entirely academic, since no one has yet seriously suggested a strategy that could get such a plan through the coming Congress anyway.—H.M.

AD-X2: The Case of the Mysterious Battery Additive Comes to an End

A brief announcement from the National Bureau of Standards discloses the end of the AD-X2 affair, a landmark in the preservation of scientific integrity against governmental whim and commercial exploitation. The case, which raged fiercely in the early 1950's, came close to shattering the bureau and aroused the nation's scientific community as it probably never was aroused before.

AD-X2 is a storage battery additive for which beneficial effects were claimed by its manufacturer, Jess M. Ritchie, of Oakland, California. Ritchie, who was closemouthed about the composition of his product, contended that, when it was properly applied to batteries, it would extend their life as much as two or three times. He said it accomplished this by reducing sulfation. His customers, in large numbers, offered enthusiastic comments on the product. The Bureau of Standards, to its misfortune, was unable to confirm these findings in laboratory tests. Its analysis showed AD-X2 to be nothing but a mixture of sodium and magnesium sulfates, the standard ingredients of additives which it had previously deemed useless. Ritchie later conceded that sodium and magnesium sulfates were indeed the principal ingredients, but claimed that his product's virtues came from certain "trace elements" which he would not disclose. The bureau said that if by trace elements he was referring to impurities normally found in these substances, AD-X2 then indeed contained trace elements. But it still could find no battery-rejuvenating powers in AD-X2. On the positive side it was able to report that Ritchie's mysterious formula—he said he and a vice president were the only ones who knew it—sometimes varied as much as 19 percent in the proportion of its two main ingredients. The bureau also found that it would cost a nickel to buy the wholesale materials for a batch that Ritchie retailed for $36. Ritchie himself was dubious of the powers of chemical analysis. He quoted his chemist as telling him that "if you had 10 chemists 30 years and they worked at it diligently, they might be able to crack it . . . ," but Ritchie himself thought this was unduly optimistic.

To the mind of Sinclair Weeks, the Secretary of Commerce of the newly elected Eisenhower Administration, the uncompromising attitude of the Bureau of Standards, one of his subordinate agencies, was deplorable. When Allen V. Astin, who shortly before had been appointed bureau director, failed to respond to suggestions that a different finding might be produced, Astin's resignation was requested. Astin complied, but was reinstated a few hours before the resignation was to become effective, following reports that some 400 scientists at the bureau would also depart. In the meantime, hearings were held before the Senate Small Business Committee. They produced little enlightenment on the question of whether AD-X2 improved batteries, but they did clearly illuminate Secretary Weeks' view of how scientific evidence was to be regarded when it conflicted with commercial interests.

In testifying on Astin's forced resignation, Weeks stated: "I am not a man of science, and I do not wish to enter into a technical discussion or be accused of overruling the findings of any laboratory. But as a practical man, I think that the National Bureau of Standards has not been sufficiently objective, because they discount entirely the play of the market place. . . . As a practical man, I do not see why a product should be denied an opportunity in the market place. I believe that the purpose of the Congress, in establishing the Bureau of Standards and in giving powers to such agencies as the Federal Trade Commission and the Post Office Department to act to prevent unfair practices and the perpetration of frauds, was that they should be operated or their powers should be exercised in the interest of the general public."

Bureau's Role

The bureau, notable for its unblemished integrity and its aloofness from publicity, was hurled into the noisy and nasty AD-X2 affair because of Ritchie's insistence that it revise a 20-year-old report which disputed the effectiveness of battery additives. Ritchie felt the report hurt him because it was quoted in the influential publications of the National Better Business Bureau and its local affiliates. Under congressional pressure which Ritchie had enlisted in his cause, the Bureau of Standards tested AD-X2 and found it no more effective than its predecessors of two decades. On the basis of these findings, the Federal Trade Commission accused Ritchie of false advertising, and the Post Office barred his product from the mails. Ritchie's congressional supporters and Secretary Weeks prevailed upon the Post Office Department to suspend the prohibition before it took effect, and Astin shortly afterward found himself before a largely hostile Senate committee, which sought to determine why a government agency was making life difficult for an enterprising small businessman.

Astin's Testimony

Astin, confronted by the task of explaining why his laboratories could not confirm the conclusions of AD-X2's satisfied customers, was somewhat in the position of a physician arguing against patent medicines to which the patient attributes curative powers.

"If it works," he told the Senate committee, "then it must have some effect on the performance of a battery. It is possible to measure battery performance with laboratory instruments. We have been able to measure no effect of this material on battery performance. . . . They must have some measurements, some consistent, logical measurements before their observations could be taken as establishing that the material is beneficial."

Astin also pointed out that following protests from Ritchie on the nature of the tests performed by the bureau, another series of tests were conducted under conditions specified by Ritchie. "None of the judges, including Mr. Ritchie and his assistant," Astin testified, "was able to tell any consistent difference between the treated and untreated batteries."

Whether there were or not, Ritchie maintained his protests that the National Bureau of Standards was not giving him a fair deal, and innuendoes were cast about to the effect that behind the bureau's findings were battery manufacturers who feared the effect AD-X2 would have on their replacement market.

To counteract the bureau findings, Ritchie put great stress on a study M.I.T. made of AD-X2 at the request of the Senate Small Business Committee. The study, he contended, supported his claims, and, fully aware of the value of an M.I.T. endorsement, he made capital of it until a terse news release from M.I.T. disclosed that, on the basis of its tests, "it was unjustifiable to conclude that the battery additive did or did not have commercial value." It added that the M.I.T. "report

and that of the Bureau of Standards indicate a difference in judgment as to the conclusiveness of limited laboratory tests. It is not unusual for objective scientific tests to be subject to different interpretations or for differences of opinion to occur in good faith."

A more direct blow against Ritchie was in store, however, from the Committee on Battery Additives of the National Academy of Sciences, which was appointed to study the controversy at the suggestion of Secretary Weeks. It stated simply that "We conclude that the relevant data now available to us regarding the effects of AD-X2 are adequate to support the position of the National Bureau of Standards that the material is without merit." This finding quickly revived the prestige of the bureau and AD-X2's fortunes thereafter failed to rise again, despite a favorable report by the Senate Small Business Committee.

Astin, in the course of his testimony, threw some light on the intriguing question of why the customers found merit in AD-X2 while the scientists did not.

"There are a number of explanations," he said, "and I am not an expert in analyzing what makes people write testimonial letters. However, there are numerous examples where people believe they are getting beneficial results from some product. Hair restorers, I think, are a very common example. It is easy to get people to believe that they get beneficial action from hair restorers, but I know of no instance where it has been found useful."

AD-X2 Process

He also pointed out that the AD-X2 treatment involved significantly more than the mere addition of powder to the battery. The powder was accompanied by a long, low-current recharge, which would normally revive most played out batteries. In addition, he pointed out, many batteries written off as "dead" have considerable life left in them, and, matching some of the spectacular claims offered by Ritchie, he reported that "some of our staff members . . . bought a lot of second-hand batteries that had been turned in as being at the end of their useful life, and did nothing to them, but just put them in their cars—they did not even charge them—and the first failure occurred after six months, according to my recollection."

Ritchie's prospects seemed to brighten a bit in 1956 when the Federal Trade Commission, after 2 years of hearings, concluded that when the scientific conclusions were balanced against the numerous reports of customer satisfaction, Ritchie could not be burdened with a charge of misleading advertising. The basis of the FTC conclusion was that if the customers felt they were getting what Ritchie claimed to give them, they were not being deceived. This decision would seem to open the way to a thriving placebo industry.

Ritchie subsequently brought suit against the Government for $2.4 million, claiming that the findings of the National Bureau of Standards had ruined his business. He dropped the suit earlier this month. In a statement noteworthy for its dispassionate tone, Astin announced that "I am pleased to report" the end of the case. He went on to state that "dismissal was requested by the plaintiff [Ritchie], the manufacturer of Battery AD-X2, after being advised in pre-trial conference of the nature of the Government's defense of the suit." The case was dismissed with prejudice, which means Ritchie cannot reopen it.

The Government has not disclosed what that defense was to be, but there are indications that it would have involved findings which the Justice Department and the National Bureau of Standards, with its understandably more than routine interest in the case, had developed in preparation for its final showdown with AD-X2.

Ritchie's attorney said the case was being dropped because Ritchie could no longer afford to see it through. Ritchie, he said, is in business on the West Coast, still makes AD-X2, and it is bought by long-standing, satisfied customers.

Today, as far as the federal government is concerned, AD-X2 stands in a sort of administrative no-man's land. The Bureau of Standards has found it worthless, the Federal Trade Commission has found that customers are satisfied that Ritchie is giving them what they pay for, and the Post Office Department carries the product through the mails without restrictions, which is just where Ritchie was back when he touched off the controversy by seeking to have his product exempted from the Bureau of Standards' blanket condemnation of battery additives.—D.S.G.

Announcements

The National Science Foundation has formed an **Office of International Science Activities** to provide federal agencies and other interested groups with staff and policy guidance on international aspects of research support, science education, and exchange of scientific information; and to develop experimental programs in international science cooperation. The new office, headed by Arthur Roe, former director of NSF's planning group for educational and international activities, will also cooperate with the Department of State in formulating a U.S. foreign policy in science and science education.

Sets of **metals abstract references** are currently available through the American Society for Metals' world information files. The 1960 files cover columbium, molybdenum, tantalum, tungsten, cryogenic properties of metals, vacuum melting and casting, nondestructive testing, explosive forming, and oxygen steel-making. Prices, commensurate with number of abstracts, range from $12 to $45. (ASM, Metals Park, Ohio)

The Soviet Ukrainian Academy of Sciences is establishing an **Institute of Cybernetics Problems** in Kiev to promote theoretical research in the development of new computing, control and information machines, and telemechanic systems. A similar institute is to be set up in Moscow under the U.S.S.R. Academy of Sciences, and a cybernetics department is being founded at the academy's Siberian branch in Novosibirsk.

A new federation of eye banks, to be known as the **Eye-Bank Association of America,** has been established by the American Academy of Ophthalmology and Otolaryngology. Objectives of the association will be to standardize the activities of eye banks, to educate the public and establish national legislation on eye donations, and to promote research in the prevention and treatment of blinding eye diseases. (Ross Guglielmino, President, Associated Eye-Banks, Rochester, N.Y.)

A recent survey of over 1000 **African students in the United States** showed that 79 percent were satisfied with their training. Nearly half of the students believed that their U.S. education would prepare them for their professional ca-

reers, but 28 percent indicated they would need practical experience or further graduate study. The survey, sponsored by the Institute of International Education, also revealed that over a third of the students were studying social sciences, 16 percent were in the physical or natural sciences, and only 9 percent were in engineering. (IIE, 800 Second Ave., New York 17. $2.50)

Highly purified **C^{14}-labeled substances** (milk fat, lactose, citrate, casein, and albumin), accumulated and preserved over a 12-year period for experiments on milk synthesis in lactating dairy cows, are currently available through the University of California. (Jack R. Luick, Department of Animal Husbandry, University of California, Davis)

Recent **National Science Foundation publications:**

Proceedings of a Conference on Academic and Industrial Basic Research (Nov. 1960, Princeton Univ.) covers the role of government, industry, and the university; the interdependence of academic and industrial basic research; managerial and personnel problems in research laboratories; and examples of industrial experience in basic research. $0.55.

Publication of Basic Research Findings in Industry, 1957–59, covers publication policies and practices of 174 companies conducting basic research. $0.25.

The Long-Range Demand for Scientific and Technical Personnel, prepared by the U.S. Department of Labor's Bureau of Labor Statistics. The report describes the method for estimating the long-range demand, and, based on presently available data, projects the estimates to 1970. $0.50. (Superintendent of Documents, Government Printing Office, Washington 25, D.C.)

Meeting Notes

The first Southeastern conference on **theoretical and applied mechanics** will be held at Gatlinburg, Tenn., from 3 to 4 May 1962. The conference, sponsored by Oak Ridge National Laboratory, will cover solid and fluid mechanics, and dynamics. (H. W. Hoffman, Oak Ridge National Laboratory, Oak Ridge, Tenn.)

A 17-day **electronics overseas seminar**, sponsored by *Electrical Design News*, will begin on 14 February 1962. Participants, limited to 30 in the electronics designing or engineering fields, will attend the Salon Internationale des Composantes Electroniques in Paris from 16 to 20 February, and will visit major electronics research and development centers in England, France, Germany, Holland, and Denmark.

Subsequent EDN-sponsored seminars will comprise engineers and designers in the aerospace, machine-tool, business-machine, and other industries. (Lawrence L. Rosine, Rogers Publishing Co., 3375 S. Bannock St., Englewood, Colo.)

The 1962 conference on **data acquisition and processing in medicine and biology** will be held from 18 to 19 July in Rochester, N.Y. Papers should reflect fundamental approaches and philosophies of diagnostic and data-enhancing methods, clinical applications, instrumentation, feasibility studies, or actual computations. Deadline for abstracts: *1 March 1962*. (Kurt Enslein, Brooks Research, Inc., Box 271, E. Rochester)

Grants, Fellowships, and Awards

Scientists who have completed residency training, or who are conducting independent clinical or basic research, are invited to apply for fellowships in **medical education research**, recently established by the American Heart Association. Selected candidates will attend one of the three medical schools that have departments of research in medical education. No fixed stipend has been established. (F. J. Lewy, AHA, 44 E. 23 St., New York 10)

Individuals and firms or other interested groups with research or development capability in **coal technology and economics** are invited to submit contract research proposals for consideration by the U.S. Office of Coal Research. Proposals (five copies) should include title, primary purpose, objectives, and estimated duration of the project; procedures to be followed; background and qualifications of personnel who would work on the project; an estimated budget breakdown covering the cost of each item and the total cost; and background information, describing the location, facilities, special equipment available, and previous research work performed in the categories covered or in related fields. (U.S. Department of the Interior, OCR, Washington 25, D.C.)

The University of Wisconsin is offering fellowships and assistantships in **educational psychology**, including human development and learning, individual diagnosis and remediation, measurement, and statistics and research design. Fellowships are $2000, $2200, and $2400 for the first, second, and third years, respectively, with an additional $400 for each dependent. Deadline: *15 February 1962*. Applications for assistantships ($1965 to $3000) will be accepted at any time. (Lindley J. Stiles, Department of Educational Psychology, University of Wisconsin, Madison 6)

Graduate traineeships in **biometry** are currently available through the U.S. Public Health Service. Stipends, which include dependency allowances, vary according to education and experience. (Executive Secretary, Advisory Committee on Epidemiology and Biometry, PHS, Bethesda 14, Md.)

For those applicants who are unable to train during the academic year, a cooperative graduate summer session on statistics in the health sciences is offered at elementary, intermediate, or advanced levels. (Lincoln Moses, Department of Statistics, Stanford University, Stanford, Calif.)

The National Science Foundation has established an **undergraduate instructional scientific equipment program**, intended to strengthen the scientific resources of smaller colleges and universities granting bachelor of science degrees. The new plan will provide funds, not to exceed $25,000, for microscopes, centrifuges, microtomes, test equipment, and similar scientific apparatus to be used in laboratory or lecture demonstrations. All grants under the program are required to be on a matching basis, with at least 50 percent of the direct costs to be derived from nonfederal sources. (NSF, 1951 Constitution Ave., NW, Washington 25, D.C.)

The University of Cincinnati's Institute of Industrial Health is offering graduate fellowships in the following programs:

Industrial medicine, leading to the

doctoral degree in the field: Stipends for the first 2 years vary from $3000 to $4000, depending on marital status. In the final or residency year, the fellow will be compensated by the organization in which he is completing his training. A 3-year academic program, leading to the D.S. degree, and a 1-year program leading to the M.S. degree, are also offered.

Environmental hygiene (industrial hygiene, wastes, and toxicology; air pollution; and other subjects), leading to the degree of D.S. in industrial health. A 1-year course is also offered for candidates for the M.S. degree. Starting stipend is $3000 for unmarried students and $3600 for married students.

All applicants must be medical-school graduates who have completed a minimum of 1 year's internship. (Secretary, Institute of Industrial Health, College of Medicine, Eden and Bethesda Aves., Cincinnati 19, Ohio)

Fellowships for graduate training in the **history and logic of science** are available at Indiana University for the 1962–63 academic year. (Marie B. Hall, 108 Social Science Building, Indiana Univ., Bloomington)

The Office of Naval Research is considering research proposals within the scope of Project SQUID—investigation of the physical and chemical processes associated with the **conversion of energy into thrust**. The project includes the preliminary exploration, analysis, and evaluation of potential aerospace propulsion systems. Deadline: *29 January 1962*. (John B. Fenn, Princeton University, Princeton, N.J.)

Grants-in-aid of research on the **ecology of the Blue Ridge Mountains' escarpment gorges** are available through the support of the National Science Foundation. (Executive Director, Highlands Biological Station, Highlands, N.C.)

The American Chemical Society is soliciting nominees for the 1962 Dexter award in the **history of chemistry**. The $1000 award will be made on the basis of publications, teaching methods, bibliographical contributions, or other services which have advanced the history of chemistry. Deadline: *10 March 1962*. (Sidney M. Edelstein, Dexter Chemical Corp., 845 Edgewater Rd., Bronx 59, N.Y.)

Scientists in the News

Gilbert H. Mudge, professor and chairman of the department of pharmacology and experimental therapeutics, and associate dean of Johns Hopkins School of Medicine, has been appointed dean of Dartmouth Medical School. He will succeed **S. Marsh Tenney**, who is resigning his administrative post in order to devote more time to teaching and research as chairman and professor of physiology.

J. Stannard Baker, director of research and development at Northwestern University's Traffic Institute, has won the $1000 Metropolitan Life award for research in accident prevention.

Glenford H. Clewett, Laurence E. Sausa, and **Lewis P. Twichell**, of the Union Carbide Nuclear Company, have each received a $1000 K. C. Li prize for advancing the science of tungsten. The award, last presented in 1957, is administered by Columbia University.

Richard E. Young, of Hercules Powder Company's chemical propulsion division, has won the 1961 Airpower Achievement Award in Research and Development. The prize, presented by the New Jersey Wing of the Air Force Association, was awarded for his development of a new case material for solid-propellant rocket motors.

Jack R. Van Lopik, former chief of the military projects section at the U.S. Army Engineer Waterways Experiment Station in Vicksburg, Mississippi, has joined the geosciences department of Texas Instruments Inc., in Dallas.

Hubert V. Pipberger, assistant professor of medicine at Georgetown University, is the 1961 winner of the Veterans Administration's William S. Middleton award for his method of analyzing electrocardiograms by means of electronic computers.

At the U.S. Atomic Energy Commission's Puerto Rico Nuclear Center:

Henry J. Gomberg, former University of Michigan director of research on the peaceful uses of atomic energy, has been appointed deputy director of the center.

F. K. S. Koo, associate scientist in the center's agricultural biosciences division and professor of genetics at the University of Puerto Rico, has been named corresponding member of the Academia Sinica Institute of Botany in Taipei, Taiwan.

Recent staff appointments at Electro-Optical Systems in Pasadena, Calif.:

Morton B. Prince, corporate vice president of Hoffman Electronics, has become manager of microelectronics.

Guntis Kuskevics, of General Electric Company, and **James A. Bittles**, of the University of Southern California, have become senior scientists.

Elizabeth B. See, formerly with the El Segundo division of Douglas Aircraft Company, has become a senior scientist in the research department of Acoustica Associates, manufacturers of ultrasonic systems.

Recent staff appointments in the University of Chicago's department of psychology:

David Bakan, of the University of Missouri, and **Robert McCleary**, of the University of Michigan, have been named professors of psychology.

Erika Fromm, of Northwestern University Medical School, has been named professorial lecturer.

Robert E. Thompson, former director of pharmacy for Armour Pharmaceutical Company, has been appointed director of Schering Corporation's pharmaceutical research and development division.

Robert G. Grenell, professor of neurobiology at the University of Maryland, is spending a year in Trivandrum, India, with the U.S. Agency for International Development. He has been assigned to Travancore University's medical college.

Walter L. Palmer, one of the original eight faculty members of the University of Chicago's school of medicine, is retiring from his post as Richard Crane professor of medicine. He will continue with the university as a clinician, teacher, and clinical investigator.

Recent staff appointments at the U.S. Public Health Service's division of air pollution:

Robert J. M. Horton, professor of epidemiology at the University of

Michigan, has become chief of the field studies branch.

David L. Coffin, pathologist for the Animal Health Center in New York, has become director of research at the division's laboratory of medical and biological sciences.

Sidney W. Fox, of Florida State University, has been named director of the university's newly formed Institute for Space Biosciences.

Bernard M. Wilner, formerly with Aerojet-General Corporation, has become principal scientist in Electro-Optical Systems' fiuid physics division, Pasadena, California.

William E. McEwen, professor of chemistry at the University of Kansas, has been appointed Commonwealth professor and head of the department of chemistry at the University of Massachusetts.

Martin W. Essigmann, chairman of dependent Laboratories' third annual has been named dean of research at Northeastern University.

Willis E. Lamb, Jr., Wykeham professor of physics at Oxford University (England) and a 1955 Nobel laureate, will become the first Henry Ford, II, professor of physics at Yale.

Charles E. Enderby, former assistant professor of electrical engineering at the University of Illinois, has joined General Electric Company's traveling-wave tube product section as a senior engineer.

Herbert M. Block, vice president of United States Testing Company, has received the American Council of Independent Laboratories' third annual meritorious service award.

Fred Alt, chief of the National Institutes of Health's instrument engineering and development branch, has been selected to organize and direct a biomedical sciences division for the Instrument Society of America.

Robert A. Norris, laboratory technician at the Irwin Memorial Blood Bank of San Francisco and an independent research ornithologist, has received the 1961 George Mercer award of the Ecological Society of America and the 1961 Harry R. Painton award of the Cooper Ornithological Society. He shares the Painton award with **Gordon L. Hight, Jr.**, of Rome, Ga.

Recent staff appointments at the U.S. Public Health Service's occupational research and training facility in Cincinnati:

Francis M. Dukes-Dubos, of the Johns Hopkins University chemistry department.

Robert C. Stroud, of the Naval Medical Research Laboratory in New London, Conn.

Alexander Cohen, of the U.S. Army Quartermaster Research and Engineering Command in Natick, Mass.

Clark M. Humphreys, of the American Society of Heating, Refrigerating, and Air Conditioning Engineers Laboratory in Cleveland, Ohio.

Awards received by staff members of the National Institutes of Health:

George Z. Williams, chief of the clinical pathology department at the NIH Clinical Center, has won the Ward Burdick award for outstanding service in pathology.

Helen M. Dyer, of the National Cancer Institute's laboratory of biochemistry, has won the Garvan medal of the American Chemical Society.

Stanley J. Sarnoff, chief of the National Heart Institute's laboratory of cardiovascular physiology, was presented an award by the Kansas City (Mo.) Heart Association for his work in cardiovascular basic research.

Philip F. Ordung and **Albert G. Conrad**, of Yale University, have been appointed professor and dean of the School of Engineering, respectively, at the University of California (Santa Barbara).

Ira Charak, former senior nuclear engineer for Chance Vought Corporation, has joined Internuclear Company, a subsidiary of Petrolite Corporation, in St. Louis, Missouri.

Paul H. Emmett, Grace professor of chemistry at Johns Hopkins University, delivered the Peter C. Reilly lectures at the University of Notre Dame during the week of 10 December 1961.

Constantine Andricos, of the W. L. Maxson Corporation, has been appointed senior engineer at PRD Electronics' products and components division in New York.

Gwynn Nettler, formerly with Dando, an industrial psychology firm in Mexico City, has been appointed senior clinical psychologist at the Nevada State Department of Health's Special Children's Clinic in Reno.

Frank M. Setzler, formerly of the Smithsonian Institution's department of anthropology, has been named director of the Southeast Museum of the North American Indian in Marathon, Florida.

Recipients of the Chicago Technical Societies Council 1961 merit awards for scientific and technical achievements:

David W. Young, research associate for Sinclair Research, Inc., at Harvey, Ill.

Piero P. Foa, professor of physiology and pharmacology at Chicago Medical School.

Leo Dolkart, electrical engineering consultant in Chicago.

Gabriel Betancur-Mejia, former Colombian minister of education, has been named to head the Organization of American States' Inter-American Task Force for Education, Science and Culture.

Recent staff appointments at the University of Oregon Medical School:

Richard W. Olmsted, of Temple University School of Medicine, will become professor and chairman of the pediatrics department.

Harold T. Osterud, of the Lane County (Oregon) Health Department, has been named associate professor of public health and preventive medicine.

Karl Meyer, professor of biochemistry at Columbia University College of Physicians and Surgeons, has received the New York Medical College award for his work in the study of mucopolysaccharides.

The New York Academy of Sciences' annual A. Cressy Morrison awards for research in natural science have been presented to:

G. Barski and **Fr. Cornefert**, of the Institut Gustave Roussy in Villejuif (Seine), France, for their work on the genetic mixing of artificially grown clone cells.

Dominick P. Purpura, of Columbia University's College of Physicians and Surgeons, for his work on the nerve organization of the cerebral cortex.

Genetics, the Core Science of Biology

Acquisition of a broader understanding of a particular branch of science may be an exhilarating experience.

Theodosius Dobzhansky

"Genetics is the core science of biology. . . . Genetics is unique in biology for its broad and fundamental theory, and for methods which provide approximate solutions of the problems posed" (Sager and Ryan, 1961). Being another geneticist, I like to hope that this prideful affirmation is warranted. It is certainly true that the interest toward genetics has increased greatly in recent years, not alone among biologists but also among other scientists and to some extent among the general public. Genetics is one of the fastest growing fields of study, and it impinges upon an extraordinary variety of problems of both the natural and social sciences, and even of the humanities. Different approaches to the field of genetics or to some of its subdivisions are represented in the fine collection of five books reviewed here: **The Science of Genetics** by Charlotte Auerbach (Harper, New York, 1961. 273 pp. Illus. $5.95); **Genetic Research** by Arne Müntzing (LTs Forlag, Stockholm, Sweden, 1961. 345 pp. Illus. S.Kr. 36); **Genetics on the Population Level** by Marianne Rasmuson (Svenska Bokforlaget Bonniers, Stockholm, Sweden; Heinemann, London, 1961. 192 pp. Illus.); **Human Genetics** by C. C. Li (McGraw-Hill, New York, 1961. 218 pp. Illus. $8.50); and **Cell Heredity** by Ruth Sager and Francis J. Ryan (Wiley, New York, 1961. 411 pp. Illus. $7.50).

The Science of Genetics, by Charlotte Auerbach, is addressed to the shadowy creature called "the general reader," but it disclaims any intention of providing a merely entertaining account of the more spectacular recent discoveries. On the contrary, it aims to give "the indispensable knowledge without which the most recent advances in genetics cannot be understood." To do this in a rather compact book, assuming no previous knowledge of biology, is really a *tour de force*, and it is remarkable how successful the brave attempt turns out to be. The order of presentation is unlike that of any other book on genetics familiar to me. The first chapter is in the form of a colloquy between a geneticist, a physician, a farmer, and a schoolboy earnestly discussing "What genetics is about." This is followed by a brief statement of the result of Mendel's work, by an equally brief introduction to chromosomes and genes, and only later by a more circumstantial account of Mendel's law of segregation, and by "A very little statistics" (without a single formula). Mendel's second law enters only in chapter 19 and is followed by a brief consideration of linkage. Eugenics is in chapter 13 and a discussion of the heredity-environment problem and of twin studies is in chapters 16 and 17. The nature of the gene and the story of deoxyribonucleic acid come in chapters 23 to 26, and the book concludes with "Evolution as seen by a geneticist." A series of simple and sometimes slyly humorous cartoons and eight plates of photographs illustrate the text.

The style of writing throughout is even, restrained, and simple, but without patronizing talking down. An attitude of judicious nonpartisanship is maintained without evading some "fighting" problems. Thus, Auerbach thinks that it is "not impossible that the genes that enable a person to excel in intelligence tests devised by Whites are more frequent among American Whites than among American Negroes," although "No reasonable conclusion can be drawn as long as there is no equality of environment and opportunity between the two groups." Dangers of genetic radiation damage are duly stressed, but the often neglected risk of genetic damage by chemical mutagens is given emphasis. Eugenical measures are endorsed in principle, but the more strident projects in this field are barely mentioned. In a book which says so much so concisely, some oversimplifications are probably unavoidable. Why human and other populations happen to carry heavy loads of harmful genes is not really comprehensible without explanation of the gene frequency concept and at least a dash of "mathematics." The conventional way of writing about genes as determining "traits" obscures the idea that the genotype determines the responses of the organism to its environments; one may well doubt that animals carry special genes which determine whether or not a heart will be formed (page 33). These few misgivings do not seriously detract from the value of the book as perhaps the most simply presented and yet solid account of basic genetics.

Emphasis on Botany

Genetic Research is an English translation (by the author himself) of the second revised Swedish edition of the text of genetics (also available in German) which is widely used, particularly in continental Europe. Coming from the pen of an eminent plant geneticist, the book properly emphasizes botanical materials and the aspects of genetics which bear on problems of plant breeding and scientific agriculture. I know of no other modern text which does this quite so thoroughly and so well. This does not mean that nonbotanical materials are neglected. Quite the contrary: *Drosophila*, the queen of genetics which some geneticists would now relegate to the position of a mere queenmother, other animals, and especially human examples are used wherever convenient. One chapter (the 21st) covers briefly the work on the genetics of bacteria and viruses. The presentation is accurate, up to date, and well balanced throughout.

Classical transmission genetics is outlined in the first two chapters, which

The author is professor of zoology at Columbia University; in 1941 he was awarded the Daniel Giraud Elliot Gold Medal by the National Academy of Sciences for his book *Genetics and the Origin of Species*, and in 1958, the Academy's Kimber Award for achievement in the science of genetics.

generally follow the historical sequence of genetic discoveries (except that the concepts of allelism, homozygosity, and heterozygosity are introduced in a chapter preceding that in which an account of Mendel's experiments is given). Sex-linked inheritance is discussed in chapter 14, that is, after linkage and the genetic maps of chromosomes (chapters 9 and 10); this is perhaps the only feature of the book which geneticists with a zoological background may find a bit contrary to their predilections. Mutation, genic and chromosomal, is discussed in chapters 16 to 19, physiological and biochemical genetics in chapters 20 to 22, population and evolutionary genetics in chapters 23 to 25 and in chapter 27, and plant and animal breeding in chapters 28 and 29. The book closes with a discussion of "Man and the laws of heredity" (chapter 30), which in my opinion is, unfortunately, the weakest chapter in an otherwise excellent book. Among the rather numerous texts of genetics now available in English, Müntzing's book is the most thorough in its coverage of the topics of particular interest to botanists and agriculturists: this probably defines its "ecological niche," although all geneticists, irrespective of their special interests, will find the book useful and stimulating.

Genetical Mathematics for Biologist Consumers

Though expanding rapidly in diverse directions, genetics is still an integrated science and preserves its logical unity. The two subdivisions of genetics which have made enormous strides in recent years are population genetics and, most notably, biochemical genetics. Rasmuson's *Genetics on the Population Level* and Li's *Human Genetics* deal, notwithstanding their dissimilar titles, with much the same subject matter, the mathematical fundamentals of population genetics. Writing mathematics for the benefit of biologists and students of medicine is a task that poses difficulties about equally staggering to mathematicians turned biologists and to biologists turned mathematicians. Many a biologist has been annoyed to read that certain formulas or equations "evidently" lead to other formulas or equations which to him look very different, and many a mathematician has been exasperated by the obtuseness of biologists who do not find these things so evident." Now, Li has shown himself in his previous books a real wizard at conveying genetical mathematics to the biologist consumer, and *Human Genetics* proves his hand has certainly not lost its skill. Rasmuson does equally well in her slightly shorter but just as rewarding book. Both authors begin with discussions of Mendelian segregations in families and of genetic equilibria in Mendelian populations. Li illustrates the genetic equilibria with amusing allegorical models of "Game of Give and Take," "The Glove Club," and "Muller's Trucking Company." Discussions of factors altering the gene frequencies then follow—mutation, selection, and migration pressures. Phenomena of inbreeding and random genetic drift in small populations are taken up next. The genetics of polygenically determined traits and correlations between relatives are discussed. Rasmuson concludes with examples of "Practical difficulties encountered in two problems of population genetics." It is a pity that Rasmuson's book does not have a list of literature references; Li gives a short but well-chosen list. So imposing has been the growth of population genetics in recent years that much of the material presented in the books by Rasmuson and Li is not to be found in older books. Of course, rapid growth of a branch of science is a two-edged sword, as far as books are concerned; the interest of new books is accentuated, but the rate of obsolescence is just as surely speeded up!

It is really a disservice to Sager and Ryan's *Cell Heredity* that its dust jacket claims the book provides "a wholly new synthesis of the field" of genetics and treats "The science of genetics as it appears today, within the framework of past findings." The authors say explicitly in their preface: "We have limited ourselves to the discussion of genetics at the cellular level." But they must be credited with a no mean achievement—a critical review and analysis of the truly magnificent advances of biochemical (or molecular, or physiological) genetics, advances which have not only transformed this branch of genetics in the last 20 years, and even in the last 10 years, but which are influencing the whole science of biology. The need for a book such as this has been keenly felt in recent years; the only other book covering very roughly the same field is *Genetics and Metabolism* by R. P. Wagner and H. R. Mitchell (1955), and a comparison of the two books suffices to show how spectacular have been the developments between 1955 and 1961.

To write a book about a new or a newly transformed branch of science means breaking new ground; an author has no precedents to follow and no old models to improve upon. Sager and Ryan have on the whole risen to the task, although it may be questioned whether the sequence of presentation they have chosen is the best possible one. The book opens with a discussion of bacterial transformations and of the chemistry of nucleic acids; this is followed by a discussion of mutation and of mutation rates in diverse organisms, from virus to man; of gene recombination, linkage, and chromosome maps; of recombination in viruses and bacteria. Chapter 6 is an excellent synthetic discussion of "What is a gene?" Then we return to recombination and to the chemistry of mutation; a chapter dealing with "Nonchromosomal genes" is intercalated; there follow discussions of gene action, of genetic control of cell integration, of genetics of somatic cells. The book closes with a perhaps too brief "Summing up."

The books of Rasmuson, of Li, and of Sager and Ryan will be most useful to graduate students and others familiar with the fundamentals of genetics. One hopes, together with Sager and Ryan, that "The acquisition of a broader understanding about a particular branch of science may be an exhilarating intellectual experience" also "to the curious-minded of all ages from college students, to mature scholars in disciplines other than genetics." Certain it is that no geneticist of any age can afford not to read and to study their book, if he wishes to be well informed about the most exciting recent developments in his field. No less certainly, the five books here reviewed show that the "core science of biology" is at present in a period of most rapid growth.

Nucleons in Nuclei

Nuclear Sizes. L. R. B. Elton, Oxford University Press, New York, 1961. 115 pp. Illus. Paper, $2.40.

This small monograph is on the subject of nuclear sizes and density distributions. Since Rutherford first noticed deviations from the point scattering formula bearing his name, the subject of nuclear sizes has been of continuing interest. Although the question of nuclear size and composition has stimulated a great deal of research,

very few reviews of the subject have been published. Thus Elton states, "The purpose of this book has been to systematize the experimental data that bear upon the density distribution of nucleons in nuclei and to correlate them, as far as possible, with current nuclear theories." He clearly succeeds in filling the gap, for the moment, in spite of the brevity of the book. He touches on virtually all the important methods of measuring nuclear sizes. Because of his own significant contributions to several aspects of the subject, Elton is able to write authoritatively about the basic methods and the quantitative results derived from them.

The important methods discussed in the order of their presentation, are electron scattering, muonic atoms, x-ray fine structure, isotope shift, mirror nuclei, semiempirical mass formula, high energy scattering of nucleons (use of the optical model), alpha scattering and alpha decay, meson scattering, absorption cross sections at high energies, and scattering of low energy neutrons. Following the discussion of methods, the author concludes with a chapter on the nuclear surface, including theory and experimental evidence.

Most subjects are covered thoroughly enough, in my opinion, in view of the incomplete or inadequate theory presently developed to account for the detailed facts of nuclear structure. A few subjects are dealt with in surprising detail for such a tiny volume. However, the method of the semiempirical mass formula for the nuclides is presented in an extremely brief way; some of the more recent work on this subject is not described, nor are recent references given. Elton does not mention a method of considerable importance, one which promises to yield much information on the mass density and neutron density distributions in nuclei, namely the method of coherent neutral pion production developed by the group at the National Bureau of Standards.

For the sake of completeness, there are a few minor points which should be mentioned. In numerous places Elton states that experimental results are based on relative cross sections rather than on absolute cross sections (pages 5, 19, and 20), whereas many of the data are in reality absolute within a somewhat larger error than indicated. Also, more recent absolute data are not given. In this respect the discussion of neutron size (page 21) is entirely out of date. Of course, this is a penalty for writing a book in a rapidly changing field. In a different context, the author sometimes gives figures and tables without mentioning the sources.

In spite of these minor imperfections, Elton has done a commendable job in collecting data and in making the subject understandable. People working in the field will find the book a necessity; others will find it interesting in many ways. It also provides a good example of how quickly a modern subject can develop in all its varied detail. I recommend the book highly.

R. HOFSTADTER
Department of Physics,
Stanford University

Mathematical Tools

Fourier Transforms and Convolutions for the Experimentalist. R. C. Jennison. Pergamon, New York, 1961. vi + 120 pp. Illus. $5.

The uninitiated can grasp the meaning of the Fourier transform by considering the behavior of a simple lens. The lens is ordinarily thought of as focusing the rays diverging from a point on an object to the corresponding point in an image, but it also focuses, at a point in the back focal plane of the lens, all rays which come from different points in the object and which are parallel to a single direction. The collection of such points in the back focal plane comprises the diffraction image of the object. In the process of focusing, rays from various points in the object (each located by the variable coordinate x) are brought together (integrated) on the diffraction image at a point located by a fixed coordinate X. Mathematically this can be expressed as $F(X) = f(x)e^{i2\pi xX}dx$. The exponential term takes care of the difference in phase of the rays arriving at the point of focus. The direction of the light can be reversed so that the roles of object plane and diffraction plane can be reversed. If this is done, a summation occurs at the object which can be expressed as $f(x) = F(X)e^{-i2\pi xX}dX$. Each of these equations represents a Fourier transformation. $F(X)$ is said to be a Fourier transform of $f(x)$, and vice versa. The relation is a beautiful one which is antisymmetrical in the phase $2\pi xX$, so that $F(X)$ and $f(x)$ are said to be conjugate and are called Fourier mates.

Jennison's book, with 110 pages of text, is short enough to be read in an afternoon. In seven chapters illustrated by 62 line drawings, it discusses the most important and useful properties of Fourier transforms.

The development of the topic includes four main features. The first is the meaning of a Fourier transform itself. A list of simple Fourier mates is included here, and the discussion is extended to two-dimensional Fourier transforms.

The next general topic is concerned with convolutions. A convolution is a kind of product of two functions. (A simple introduction to convolutions is through image theory [see M. J. Buerger, *Z. Krist.*, in press].) Its relation to Fourier transforms is given by the important theorem which may be stated as *the transform of a product is equal to the convolution of their transforms.* Jennison develops this important connection and thus provides a second stage in the discussion of Fourier transforms.

The third stage concerns the differentiation of Fourier transforms, and the author shows that the differential of a transform, $f(x)$, is its mate, $F(X)$, times the factor $i2\pi X$. This leads to the notion of a differential operator and later to an integral operator. The fourth and last facet of the discussion is the autocorrelation function.

The theoretical part of the development is interspersed, somewhat irregularly, with practical applications and is amply illustrated by line drawings. The book should be read by all who have any use for Fourier transforms. Nevertheless, it is not always easy to understand, and probably will be unintelligible to anyone who has not encountered Fourier transforms. For example, the first sentence of the book is "To the question 'what is a Fourier transform?' we may most simply reply: 'A method whereby we may obtain the variation of a quantity as a spectral function (e.g. plotted against frequency) from the variation of the quantity as a function of period (e.g. plotted against time).' " This and the following four pages are nonsense to the uninitiated. Only on the fifth page does Jennison briefly define the Fourier transform with an equation. The title informs the reader that this book is directed to the experimentalist, but it turns out that the experimentalist in mind is specifically one interested in electronics, for most of the examples come from that field. If the reader is not familiar with electronic jargon, he will not understand some of the text. While there are also

some optical examples, the obvious relation of Fourier transforms to diffraction is nearly ignored. In spite of the book's elementary nature, I do not recommend it to those without some previous knowledge of Fourier transforms. The fundamental theorems are not proven but merely stated. The quality of the teaching is often poor. To those with some background, however, it is interesting, especially in showing the relations between some simple Fourier mates, and it is also stimulating in bringing together the useful fundamental properties of Fourier transforms.

M. J. BUERGER

Laboratory of Crystallography, Massachusetts Institute of Technology

Experimental Technique

Carbon-14 Compounds, John R. Catch. Butterworth, Washington, D.C., 1961. viii + 128 pp. Illus. $5.50.

John Catch's *Carbon-14 Compounds* is a welcome addition to the literature. Com[illegible] a dozen years after Calvin's pioneering, and now classic, *Isotope Carbon*, it takes careful measure of the intervening growth of what is still an art—the art of putting carbon-14 into complex organic compounds, applying these in tracer experiments, and assaying the results. The form of the book reflects the subject matter, which is abundant in detail but intractable in form.

The author is associated with the Radiochemical Centre of the United Kingdom Atomic Energy Authority, and he knows what should and what should not be included in a treatise of this sort. The result is practical, concise, and well balanced.

The first chapter deals with the production of C^{14} via the N^{14} (n,p) C^{14} reaction. Included is a discussion of the incorporation of C^{14} in organic materials by the direct neutron irradiation of nitrogen containing organic compounds; this discussion covers the work of Libby, Wolf, Yankwich, and Zifferero, among others. The incorporation of C^{14} by chemical synthesis and biological methods of labeling is covered in the next two chapters. Here, as elsewhere in the book, the bibliographies are unusually complete. For example, 203 references to journal literature appear at the end of the chapter on chemical synthesis. At that, the author makes no attempt to provide an exhaustive compilation, as the articles cited have been chosen to illustrate the text.

Catch then turns to consideration of a number of topics in a chapter entitled "Peculiar features of carbon-14 compounds." These topics include isomerism; double labeling; isotope asymmetry; rearrangements, exchange, and degradation reactions; behavior of small quantities; isotope effects; radiation decomposition; and nomenclature of carbon-14 compounds. This recital of the various special problems connected with the successful and accurate use of isotopic tracers is especially worthwhile.

A short chapter on analysis (including carrier dilution analysis), a quite complete chapter on the measurement of C^{14}, and a chapter containing some cogent remarks about precautions in the use of C^{14} compounds complete the presentation.

Anyone who is about to use C^{14} for the first time, or who has used this important isotope only occasionally, should not fail to read this book. Workers already in the field will be pleased with the extensive bibliographies. I recommend it also to undergraduates as collateral reading, for the insight it gives into an important experimental technique as well as into the subject of organic chemistry itself.

R. C. ANDERSON

Brookhaven National Laboratory, Upton, New York

Miscellaneous Publications

(Inquiries concerning these publications should be addressed, not to Science, *but to the publisher or agency sponsoring the publication.)*

The Food Economics of Urban Middle Africa. The case of Ghana. Thomas T. Poleman. Food Research Inst., Stanford Univ., Stanford, Calif., 1961. 53 pp. Illus. $1.50.

A Guide to Fortran Programming. Daniel D. McCracken. Wiley, New York, 1961. 96 pp. Illus. $2.95.

Guidelines for Preparation Programs of Teachers of Secondary School Science and Mathematics. Recommendations of the Teacher Preparation-Certification Study of the National Association of State Directors of Teacher Education and Certification and the American Association for the Advancement of Science. AAAS, Washington, D.C., 1961. 36 pp. Report of a study supported by the Carnegie Corporation, New York.

Handbook of Electronic Charts and Nomographs. Allan Lytel. Bobbs-Merrill, Indianapolis, Ind., 1961. 58 pp. Illus. $4.95.

Industrial Transistor and Semiconductor Handbook. Robert B. Tomer. Bobbs-Merrill, Indianapolis, Ind., 1961. 254 pp. Illus. $4.95.

Laboratory Manual of Vertebrate Embryology. Roberts Rugh. Burgess, Minneapolis, Minn., 1961. 292 pp. Illus. $4.

NLL Translation Bulletin, vol. 3, Nos. 3–5. National Lending Library for Science and Technology, Department of Scientific and Industrial Research, London, 1961 (order from Her Majesty's Stationery Office, Box 569, London). Annual subscription, £2 13s.; single copy, 4s. 5d. Formerly entitled **LLU Translation Bulletin**, No. 3 contains a list of approximately 300 academies and research institutes in and near Moscow; No. 4, approximately 250 planning and design institutes, laboratories, and higher educational institutions in and near Moscow; and No. 5, information concerning 155 libraries of the Academy of Sciences of the U.S.S.R.

The National Peril. A statement by the NPA International Committee. Where we stand in national defense. Franklin A. Lindsay. National Planning Assoc., Washington, D.C., 1961. 61 pp. Paper, $1.

Permanent Peace. Walter Millis. Center for the Study of Democratic Institutions, Santa Barbara, Calif., 1961. 31 pp. Single copy, free.

Some Commercial Autocodes. A comparative study. A.I.P.C. Studies in Data Processing, No. 1. E. L. Willey *et al.* Academic Press, New York, 1961. 60 pp. $2.50. Published for the Automatic Programming Information Centre, Brighton College of Technology, England.

Symposium on the Metabolism and Function of the Fat-Soluble Vitamins A, E, and K. *American Journal of Clinical Nutrition*, vol. 9, No. 4, pt. 2. National Vitamin Foundation, New York, 1961. 116 pp.

Technical Information in the U.S.S.R. Aram S. Melik-Shakhnazarov. Translated by Boris I. Gorokhoff. Massachusetts Institute of Technology Library, Cambridge, Mass., 1961. 122 pp. $1.60.

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On the Mechanism of Diamond Formation

Diamonds form by the shock-conversion of graphite, but not by decomposition of metal carbides.

Michael E. Lipschutz and Edward Anders

In an earlier report (*1*) we concluded, on the basis of a metallographic study, that the diamonds in the Canyon Diablo meteorite were formed during impact with the earth. Specifically, we suggested the following alternative mechanisms for diamond formation:

1) The direct, solid-state transformation of graphite by the impact shock.

2) The growth of diamond from an iron carbide, iron sulfide melt (i) as a stable phase under the high pressures of the impact shock; (ii) as a stable phase under localized stresses (these could result either from the unequal thermal expansion of cohenite [meteoritic Fe_3C], kamacite [α-iron], or troilite [FeS] or from the volume expansion on fusion of troilite); or (iii) as a metastable phase under localized stresses like those listed above except that the maximum pressure would be below the graphite-diamond transition pressure.

In regard to the laboratory production of diamond, we also pointed out that formation of diamonds should be thermodynamically possible not only through the decomposition of iron carbide melts but also through the solid-state decomposition of cementite (Fe_3C) and thermodynamically similar metal carbides under high static pressures.

Recently, the direct, solid-state transformation of graphite was verified by DeCarli and Jamieson (*2*), who succeeded in converting graphite to diamond by shock.

The first two mechanisms proposed for the growth of diamond from an iron carbide, iron sulfide melt are essentially similar to the General Electric Co. process of diamond synthesis (*3*) and, except for identification of the sources of pressure, may therefore be regarded as confirmed. In this report we describe results of experiments designed to test (i) the third mechanism proposed for the growth of diamond from an iron carbide, iron sulfide melt and (ii) the solid-state decomposition of metal carbide under high static pressures.

In the first series of experiments we attempted to grow diamonds metastably by allowing iron carbide, iron sulfide melts to decompose spontaneously at atmospheric pressure. In the second series, we subjected solid iron carbides and nickel carbides to static pressures above the diamond-graphite equilibrium line for extended periods. The rationalization underlying both groups of experiments is illustrated in Fig. 1 [Fig. 2 of our previous report (*1*), which gives the stability fields of graphite, diamond, and cementite in the presence of excess α-iron, with the pressure and temperature conditions of our experiments indicated].

As pointed out previously (*1*), the abscissa of this figure may be in error by as much as 300°K because of an uncertainty in the standard enthalpy of formation of cementite. Indeed, commonly accepted values of temperature *B* (the temperature, at a pressure of 1 atmosphere, at which the free energy of decomposition of cementite to γ-iron and graphite equals zero) lie from 200° to 400° to the right of the point shown in Fig. 1 (*4*). For this reason our experiments on cementite were conducted in the region to the right of the calculated cementite stability line.

We further pointed out in our earlier report that this figure is illustrative of the general phase diagram describing the decomposition of all metal carbides having small, positive free energies of formation. Because of its low thermodynamic stability, Ni_3C [$\Delta H°_f$ = 11 kcal/mole, as compared with 5.0 kcal/mole (*5*) for Fe_3C] looked particularly promising for investigation and was therefore included in the study reported here.

The failure of diamond to form under conditions where it is thermodynamically stable can be due to slow nucleation, slow crystal growth, or some combination of these factors. The crystal-growth process is usually diffusion-controlled, and thus semiquantitative estimates of expected growth rates can be made. Nucleation rates are more difficult to predict, however, and we therefore attempted to eliminate this factor in some of our experiments by seeding with diamond. To establish whether any growth had taken place, we included some C^{14}-labeled Fe_3C in our reaction mixture (*6*). The specific activity of the nondiamond carbon in the mixture was of the order of 5.8×10^5 disintegrations per minute per gram; hence, the growth of as little as 10 micrograms of diamond could be readily detected by beta counting.

The Experiments

Cementite was prepared by fusing spectroscopically pure iron in a plumbago crucible and casting the melt into a graphite mold at 1550°C. The resulting alloy was found to contain 3 percent carbon—that is, 45 percent Fe_3C. A sample of this alloy was then reduced to shavings suitable for use in the pressure apparatus. An x-ray pattern taken of the shavings revealed only α-iron and Fe_3C. No impurities could be detected on spectrographic analysis, and no residue remained on dissolution of the shavings at room temperature with 6*N* hydrochloric acid.

Carbon-14 labeled cementite was prepared by fusing C^{14}-labeled graphite, spectrographic carbon, and electrolytic iron in a water-cooled copper arc furnace (*7*). X-ray examination of this sample (37 percent Fe_3C) showed the presence of only cementite and α-iron.

To prepare nickel carbide, weighed samples of NiO were reduced at 250°C by passing a stream of H_2 gas over the powder at a rate of 0.1 liter per hour until the loss in weight corresponded to that calculated by the stoichiometric reaction. The metal powder was then carburized at 250°C with CO gas (*8*)

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Table 1. X-ray pattern of insoluble fraction from high-pressure experiments compared with patterns of chromite (*18*) and diamond *d*, Spacing between lattice planes; *I*, intensity; *hkl*, Miller indices.

Observed			Chromite		Diamond	
d	*I**	*hkl*	*d*	*I*	*d*	*I**
4.7	*vw*	111	4.80	50		
3.20	*vw*					
2.90	*w*	220	2.93	60		
2.72	*w*					
2.49	*s*	311	2.499	100		
2.37	*vw*	222	2.390	*vf*†		
2.27	*vw*					
2.22	*vw*					
2.15	*vw*					
2.06	*m*	400	2.070	70	2.07	*vs*
1.58	*w*	511	1.592	90		
1.46	*m*	440	1.461	90		
		135	1.398	*vf*†		
		130	1.310	20		
1.25	*vw*	553, 622	1.261	50	1.26	*m*
1.20	*vw*	444	1.196	30		
		155, 117	1.158	30 20		
1.11	*vw*	642	1.107	30		
1.09	*vw*	731	1.079	60	1.075	*mw*
1.04	*vw*	800	1.035	30		
		110, 114	0.975	20		
		111, 157	0.956	40		
		120	0.927	30		
					0.890	*w*
		139	0.869	30		
		112	0.846	60		
					0.819	*m*
		134, 150	0.811	10		
		159, 377	0.801	40		

* In increasing order, the intensities are *vw*, *w*, *mw*, *m*, *s*, *vs* (very weak, weak, medium weak, medium, strong, very strong). † Very faint.

Table 2. Decomposition of Fe_3C in FeS melts at atmospheric pressure.

Run	Sample	Temperature (°C)	Time (min)	Count rate of residue (count/min)	Conversion to diamond (%)
A7	Iron-rich FeS, Fe_3C	1040 ± 20	25		
A9	Iron-rich FeS, Fe_3C	1030 ± 20	25		
A12	Troilite, Fe_3C^{14}, diamond	1000 ± 25	25	0.02 ± 0.03	≦0.004
A14	Troilite, Fe_3C^{14}, diamond	1025 ± 25	15	0.10 ± 0.03	≦0.005

Table 3. Solid-state decomposition of Fe_3C at elevated pressure and temperature.

Experiment No.	Pressure (kilobar)	Temperature (°K)	Time (hr)	Count rate of residue (count/min)	Conversion to diamond (%)
P7	35 ± 2	823 ± 5	72		
P8	35 ± 2	873 ± 5	48		
P9	35 ± 2	923 ± 5	69		
P13	30 ± 2	565 ± 5	64		
P14	30 ± 2	650 ± 5	65		
P15	35 ± 2	730 ± 5	65		
P16	35 ± 2	773 ± 5	70		
P18	29 ± 2	733 ± 5	72		
P19	25 ± 2	733 ± 5	72		
P20	18 ± 2	733 ± 5	72		
P43	48 ± 2	648 ± 5	240	0.3 ± 0.1	≦ 0.2
P43 (recycle)				0.03 ± 0.04	≦ 0.01

at a flow rate of 0.1 liter per hour. Nitrogen, at the same flow rate, was used during periods of cooling and heating to prevent carbonyl formation. The sample was periodically removed for weighing in order to determine the carbon content. After carburization for 281 hours, the increase in weight of the best sample corresponded to the increase to be expected with a carbon content of 4.50 percent or a Ni_3C content of 71 percent. X-ray examination of the resulting powder revealed only Ni_3C and Ni. No residue remained after dissolution of the powder in 6*N* HCl at room temperature.

The samples were mounted on aluminum plates (0.63 mm thick), covered with Mylar film (0.9 mg/cm^2), and counted in a Sugarman type β proportional counter with a gold-plated Mylar window (1.5 mg of gold per square centimeter). The counter was shielded with 5 centimeters of lead and 0.6 centimeter of aluminum. The samples were usually counted at 2 or 5 millimeters from the counter window.

Daily background counts were taken for several weeks before and after the sample counts. The variations were strictly statistical, and thus the background correction could be determined with high accuracy. In the two geometries used, the background counts were 6.04 ± 0.02 and 6.18 ± 0.03 counts per minute, respectively.

Absolute counting efficiencies were difficult to determine, in view of the highly nonuniform particle-size distribution of the samples. Owing to the very low energy of the C^{14} beta radiation, self-absorption effects were large even for particles of fractional-millimeter size. Conservative estimates of the counting efficiencies are 4 and 3 percent for the two geometries used. The percentage of recovery for any diamond present could not be determined directly but was estimated to be greater than 50.

The experiments at atmospheric pressure were conducted by fusing iron sulfide (both artificial and meteoritic) to which iron carbide (5 to 10 percent) had been added, at temperatures ranging from 975° to 1075°C for periods of 15 to 30 minutes and cooling to room temperature within a few minutes. Fusions were made in crucibles of various materials (Vycor, porcelain, recrystallized Alundum, and meteoritic iron), under fluxes of KCl, and in a vacuum. Decomposition of the carbide

was virtually complete during this time. The extrapolated times for graphitization of diamond at these temperatures range from 1700 to 180 years (*9*, *10*) so there was no danger of graphitizing any diamond which might form. The cooled melt was then dissolved in HCl, and the residue was treated with $HClO_4$ to dissolve the graphite (*11*). Any solid material remaining was then x-rayed. We observed no lines attributable to diamond.

In several experiments, diamond seed and Fe_3C^{14} were added. In no such case did the final residue yield a count appreciably higher than the background level. The added C^{14} had counting rates of 2500 to 3000 counts per minute, whereas the observed counting rates were of the order of 0.1 ± 0.1 count per minute above the background level.

The pressure apparatus used in the experiments at elevated pressure was of the "simple squeezer" type (*12*). Cemented chromium carbide pistons were used exclusively. The powdered sample (usually 40 to 50 mg) was placed inside a washer sandwiched between two pieces of metal foil (Fig. 2). Initially, platinum-rhodium foil (Rh, 10 percent) 0.03 millimeter thick was used to contain the samples, but because this foil was difficult to dissolve, pure platinum foils were substituted. In order to preclude possible undesirable side reactions with platinum, a few duplicate experiments were performed with copper foil (Cu, 99.9 percent) or low-carbon steel. Since no difference in results was observed, pure platinum foil was used exclusively in the remainder of the experiments.

The washers were usually of case-hardened pure iron, although stainless steel washers were initially used. These latter were found to have a large chromium content which unnecessarily complicated the thermodynamic situation [$\Delta F°_{298}$ for the formation of Cr_4C = −16.8 kcal/mole (*5*)], and therefore the pure iron washers were substituted. A few experiments were run with pure copper washers, but these washers were not able to withstand the stress, and the sample extruded out. In many of the experiments we found that the sample, foil, and retaining washer were "welded" together and could not be separated. In these cases the entire assembly was dissolved.

After the experiment had been completed, the sample was removed and partially dissolved in concentrated HCl

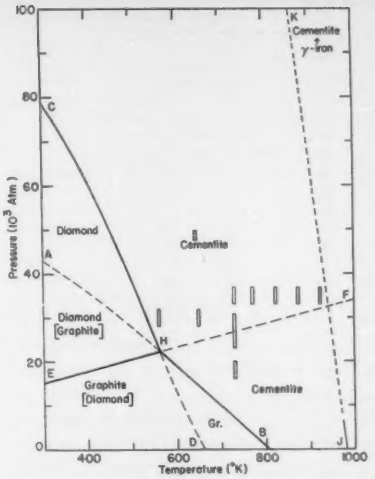

Fig. 1. Pressure-temperature conditions for Fe_3C experiments.

at about 90°C. Enough concentrated HNO_3 was then added to dissolve the foil, and the heating was continued until the reaction was complete. The residue was centrifuged, washed, and dried. It was then heated for 6 hours in an atmosphere of Cl_2 at 450°C, washed, and separated into a light ($d \leq 2.9$) and a heavy ($d \geq 2.9$) fraction by means of bromoform.

Control experiments in which diamond seed (of 3- to 6-μ diameter) were used revealed the somewhat surprising fact that the diamond was quantitatively recovered in the light phase. Apparently the light phase consisted either of submicrocrystalline graphite growing on diamond centers or of an intimate mixture of graphite carbon and diamond. No crystalline material was detected in the heavy fraction.

The two fractions were then washed with acetone, mounted on the end of a

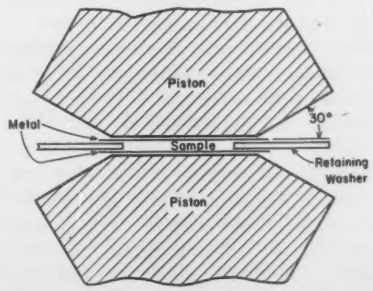

Fig. 2. Schematic arrangement of sample assembly in the pressure apparatus. [Courtesy *Am. J. Sci.*]

Lusteroid rod coated with a solution of linseed oil (50 ml of oil per 100 ml of solution) in carbon tetrachloride, and x-rayed. Since the diffraction pattern of diamond would appear if the diamond were present at levels higher than about 4 to 5 percent, as little as 5 micrograms (corresponding to 5-percent conversion) could have been unambiguously detected.

In some cases one or more diffraction lines were observed at spacings corresponding to those of diamond (Table 1). The two fractions of these runs were then further treated in one of the following ways.

Light fractions were heated for 1 hour with a solution of KNO_3 in concentrated H_2SO_4—a treatment which has been used by Wentorf (*13*) in oxidizing graphite while leaving diamond unaffected. In our early experiments, light fractions were treated with perchloric acid to destroy graphite (*10*, *11*). Although this treatment did not seem to affect polycrystalline meteoritic diamond lumps or diamond powder of particles 3 to 6 microns in diameter, the possibility remained that very finely powdered diamond of very small crystallite size might be attacked by the perchloric acid (*14*). Sarma and Mayeda (*15*) later observed this to be the case. For this reason, we avoided perchloric acid like the plague in later runs.

All heavy fractions of the Fe_3C runs (experiments P7 to P20) showed six to twelve unidentified lines in addition to three lines in the correct positions for the three diamond lines observable with FeKα radiation. This fact caused us to feel some elation, which was soon tempered by the discovery that all of these lines were due to chromite (*16*). Apparently, diffusion of Fe through the platinum foil was rapid enough to permit formation of chromite at the foil-piston interface. In subsequent x-ray work, CuKα radiation was used. With the latter source two additional spacings of diamond appear, which are not duplicated in the chromite pattern (*17*, *18*). When these lines were used as the criterion, no positive identification of diamond was made in any of the Fe_3C runs.

The heavy fractions of Ni_3C and Ni_3C–Fe_3C were found to contain a great deal of ignited chromic oxide, evidently an oxidation product of the chromium carbide piston. This oxide was found to be unaffected by fusion with $KHSO_4$ but was dissolved by evap-

Table 4. Solid-state decomposition of Ni_3C and Ni_3C–Fe_3C mixture at elevated pressure and temperature.

Experiment No.	Pressure (kilobar)	Temperature (°K)	Time (hr)	Count rate of residue (count/min)	Conversion to diamond (%)
P29	35 ± 2	823 ± 5	65		
P33	35 ± 2	950 ± 5	67		
P34	45 ± 2	743 ± 5	67		
P35	37 ± 4	958 ± 5	90		
P36	50 ± 2	648 ± 5	90		
P37	43 ± 2	848 ± 5	65		
P38	43 ± 2	843 ± 5	350		
P41	43 ± 2	843 ± 5	184	0.29 ± 0.03	≦ 0.1

oration with HF in the presence of CrO_3 (*19*). In these experiments x-ray examination revealed faint lines occurring at positions corresponding to the principal spacings of chromite. It is evident, therefore, that some chromite had formed, probably by reaction between the washer and piston, and that at least part had survived the chemical treatment described above.

Discussion

Decomposition of cementite melts at atmospheric pressure, in the absence of diamond seed, never revealed an x-ray pattern attributable to diamond (Table 2). In those cases where C^{14} had been added, the counting rate observed was not appreciably higher than the background level. It would thus appear that no diamond formed at atmospheric pressure through a metastable-phase mechanism. To the extent that these conditions were representative of those in the Canyon Diablo impact, the conclusion that the Canyon Diablo diamonds did not form as a metastable phase seems justified.

The experiments carried out at elevated pressure, with their results, are listed in Tables 3 and 4 and illustrated in Figs. 1 and 3. The rectangles shown in Figs. 1 and 3 represent experimental uncertainties in pressure and temperature. One of the experiments listed in Table 4 and illustrated in Fig. 3 was carried out with a mixture of Ni_3C (80 percent) and Fe_3C^{14} (20 percent). The thermodynamic behavior of this system should be similar to that of pure Ni_3C, and since the diffusion rate of the carbon is likely to be higher than the rate of precipitation, the C^{14} was expected to act as a tracer for the whole system. In no case did we obtain evidence of the growth or formation of diamond. True, a slight positive counting rate was observed in some of the tracer experiments (Nos. P41 and P43), but whenever these samples were recycled (experiment P43), the activity disappeared. Apparently, the activity was contained in traces of graphite carried through the procedure, and it seems likely that recycling of the remaining samples would have brought the activity down to background levels.

Similarly, none of the x-rayed samples showed evidence of diamond, once allowance was made for interference by chromite.

It now has to be shown that the negative results of the experiments listed in Tables 3 and 4 were not due simply to a low rate of carbide decomposition. That the carbide did indeed decompose is proved by the observation that all high-pressure runs yielded crystalline graphite, whereas samples of the original materials, Fe_3C and Ni_3C, treated by the same chemical procedures yielded no residue. Thus, the presence of appreciable amounts of graphite indicates that the carbide had decomposed to a significant degree (*20*). Consequently, the value given in the literature for the standard enthalpy of formation of cementite [$\Delta H^\circ_{298} = 5.0$ kcal/mole (*5*)] must be too low, as we conjectured in our previous report, and the lines *AB* and *CD* in Fig. 1 should be shifted to the right by a few hundred degrees. This shift expands the field in which decomposition of cementite can occur.

These experiments are gratifying inasmuch as they confirm the view, expressed in our previous report, that graphite can form as a metastable product above the graphite-diamond equilibrium line. They are disappointing inasmuch as we have been unable to channel this decomposition in the direction of the stable reaction product, diamond. Just why the metastable product graphite is favored even at high pressures is a matter of conjecture. Submicroscopic graphite nuclei were probably present in the original material in such large numbers as to favor the graphite path overwhelmingly. Moreover, it is conceivable that the added diamond crystals could not act as effective nucleation centers, owing to surface effects. Perhaps future experiments should be designed to take both possibilities into account.

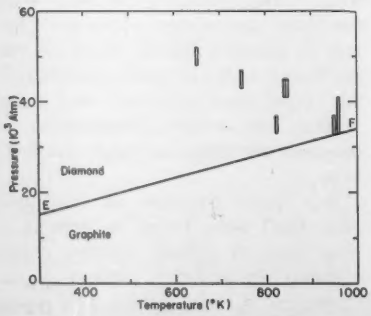

Fig. 3. Pressure-temperature conditions for Ni_3C experiments.

Conclusions

In none of our experiments were we able to observe any evidence of diamond formation or growth. It thus appears unlikely that the metastable-phase mechanism was of importance in the formation of the Canyon Diablo diamonds. The discovery of coesite in the sandstone of Meteor Crater (*21*) and the successful laboratory conversion of graphite to diamond by explosive shock (*2*) seem to favor the mechanism of a direct conversion of graphite to diamond by the impact shock. Further, we found that the direct solid-state decomposition of cementite at pressures below 45 kilobars and temperatures of 650° to 1000°K does not yield diamond in times of about 1 week (*22*).

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5 September 1961

Immunological Studies of Gastrin

Abstract. Hog gastrin prepared by the Gregory method stimulates antibody production in rabbits. Rabbit anti-hog gastrin serum which was reacted with hog, dog, and human gastrins in vitro caused reduction of their gastric stimulatory effect, indicating a biological cross reaction among these species.

The existence of the antral hormone gastrin was postulated by Edkins (*1*) in 1906, but Komarov (*2*) was the first to obtain an active substance from the protein fraction of antral mucosal extracts. Subsequently, other workers (*3*, *4*) have obtained substances capable of stimulating gastric secretion from the protein fraction of mucosal extracts prepared by various methods.

We have produced rabbit antibodies to hog gastrin which inhibited the gastric secretory effect of hog, dog, and human gastrin.

Gastrin was prepared from hog antral mucosa by the method of Gregory and Tracy (*4*). The final extract was lyophilized, and approximately 1.0 g of the dry powder was obtained from 1 kg of mucosa. In addition to gastrin, this product contains a quantity of inert protein and inorganic salts. It promotes a flow of acid gastric juice when given by subcutaneous injection to dogs with a gastric fistula or Heidenhain pouch.

Table 1. Data of secretory inhibition experiments. Each value recorded represents the average of two or more determinations.

Dose	Output HCl (meq/3 hr)	Reduction (%)
Hog gastrin (50 mg)	1.55	
Hog gastrin (50 mg) + rabbit anti-hog gastrin serum (3 ml)	0.61	61
Hog gastrin (50 mg) + rabbit anti-hog gastrin serum (6 ml)	0.51	67
Hog gastrin (50 mg) + normal rabbit serum (3 ml)	1.29	17
Hog gastrin (50 mg) + rabbit anti-hog Group A substance serum (3 ml)	1.32	15
Dog gastrin (75 mg)	3.53	
Dog gastrin (75 mg) + rabbit anti-hog gastrin serum (3 ml)	0.90	75
Human gastrin (30 mg)	1.08	
Human gastrin (30 mg) + rabbit anti-hog gastrin serum (3 ml)	0.39	64
Human gastrin (30 mg)	1.92	
Human gastrin (30 mg) + normal rabbit serum (3 ml)	1.87	3
Histamine phosphate (1 mg)	1.93*	
Histamine phosphate (1 mg) + rabbit anti-hog gastrin serum (3 ml)	2.06*	

* Output in 90 minutes.

New Zealand rabbits (weight, approximately 2.5 kg each) were injected in the four foot pads and the lateral thoracic wall skin with 30 mg of hog gastrin incorporated in complete Freund's adjuvant. Four to six weeks later each rabbit received a booster injection (20 mg of gastrin dissolved in distilled water) subcutaneously in the interscapular region. One week later animals were bled by sterile intracardiac puncture, and the serum was harvested. With merthiolate added as a preservative, the serum was stored at −20°C until used. The anti-hog gastrin titer of this serum was determined by the qualitative preciptin method of Heidelberger and Kendall (*5*); the average titer was 1/5000 to 1/10,000. Higher titers could be obtained with subsequent booster injections.

Agar gel diffusion experiments were performed according to the method of Wilson and Pringle (*6*). Plates were prepared, allowed to stand in a moist chamber at 37°C for 7 days, and then read.

Biological inhibition tests were performed in the following manner. Solutions of hog, dog, and human gastrin preparations were mixed with rabbit antiserum to hog gastrin and allowed to stand overnight in the refrigerator. The mixtures were then injected subcutaneously into dogs with a Heidenhain pouch, and the secretory responses were compared with those obtained by injecting the same doses of gastrin alone. The volumes of solution injected were equal in all cases. A control injection of gastrin reacted with normal rabbit serum (Difco Laboratories) was included in all inhibition experiments.

Secretion in response to the subcutaneous injection of gastrin normally starts within 30 minutes after the injection and has practically ceased after 3 hours. Accordingly, gastric juice was collected over a 3-hour period after the injection, and the total output of hydrochloric acid during this period was determined by titration with 0.1*N* sodium hydroxide with phenol red indicator.

Table 1 presents the data of several secretory inhibition experiments. Each value recorded represents the average of two or more determinations with the gastrin preparations indicated.

Incubation of 50 mg of hog gastrin with 3 ml of rabbit antiserum to hog gastrin caused a 61-percent reduction in the acid secretion produced by 50 mg of hog gastrin alone, and the reduction was slightly greater when the hog gastrin was incubated with 6 ml of serum. In contrast with this, incubation of gastrin with normal rabbit serum produced only a 17-percent reduction in secretion. That this reduction represents a nonspecific action of rabbit serum is suggested by the similar reduction achieved by incubation of hog gastrin with rabbit anti-hog Group A substance serum (Ortho Corp.). Gastrin prepared from dog and human stomachs was also reacted with rabbit anti-hog gastrin serum, and the secretory response was reduced by 75 percent and 64 percent, respectively.

To exclude the possibility that the anti-gastrin serum was producing inhibition of secretion by some mechanism other than the inactivation of gastrin, a portion of serum was incubated with a solution of histamine, and the mixture was injected subcutaneously. Rabbit anti-hog gastrin serum failed to depress the acid secretion induced by histamine.

The reaction of hog gastrin to rabbit anti-hog gastrin serum was studied in agar gel diffusion plates. One major antigenic component and at least three minor antigenic components were demonstrated, emphasizing the impurity of gastrin prepared by this method. Dog and human gastrin reacted with homologous rabbit antiserum similarly showed multiple antigenic components. An attempt was made to demonstrate a cross reaction between hog, dog, and human gastrins when they were reacted with rabbit anti-hog gastrin serum. No such cross reaction could be shown in agar gel diffusion plates in spite of the cross reaction achieved in the inhibition experiments described above. These results may be interpreted to mean that the active secretory principle in gastrin prepared by the Gregory method is in too low a concentration to form a cross-reacting precipitin band demonstrable by the relatively insensitive agar gel diffusion method (*7*). Another interpretation might be that not all antigen-antibody complexes precipitate, particularly if the antigen molecule is small or has only one antigenic site. Thus, gastrin may be a small, univalent, antigenic molecule.

The following conclusions are suggested. Gastrin produced by the Gregory method is a relatively impure substance with several demonstrable antigenic components. The active acid secretory principle contained in this preparation may be in low concentration or may be a small, univalent antigen which does not stimulate the production of precipitating antibody. Antiserum reacted with crude hog gastrin is capable of neutralizing the physiologic effect of hog, dog, and human gastrin, illustrating a cross reaction among the species mentioned. Gregory's method of preparing gastrin almost certainly excludes contamination of the final product with histamine which stimulates gastric secretion. However, the possibility that trace amounts of histamine might be present has been considered despite the fact that biologic assay does not reveal any histamine (*4*). The present experiments add further evidence that, in gastrin prepared by the Gregory method, histamine is not the substance that induces acid secretion (*8*).

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Erythrocyte Automosaicism in Some Persons of Known Genotype

Abstract. We have estimated the proportions of non-A and non-B erythrocytes in some members of four families in which both parents were blood group AB, including two B homozygotes. The exceptional cell frequencies were not discernibly correlated with age. The B homozygotes had fewer non-B exceptional cells than their AB parents or sibs, but too many to represent independent losses of the B alleles. These results are not in agreement with the simplest expectations based on the mutational hypothesis of automosaicism.

Red cell populations in human A or AB individuals and in *Phaseolus* lectin-positive pigeons are heterogeneous, containing a proportion of non-A or lectin-negative cells that is rather stable, but subject to individual variation. This proportion is increased by P^{32} treatment in man or by whole-body x- or gamma irradiation in pigeons (*1*). Part of the induced increase is stable for an indefinite time, which suggests that the phenotypic heterogeneity among the red cells reflects a corresponding genetic diversity among the reproducing erythropoietic cells. The presence of such exceptional cell populations generated within an individual has been called automosaicism to distinguish it from chimerism involving admixture of cells from different zygotes.

Two criteria bearing on the spontaneous origin of automosaicism are its relations to age and to zygosity. If it is mainly caused by accumulation of genetically altered stem cells during adult life, a correlation with age is expected. If it is caused by independent events affecting the two ABO alleles in the diploid cell, then the proportion of exceptional cells in a homozygote should approximate the square of the proportion in a comparable heterozygote.

Through the cooperation of the Chicago Blood Donors Association, we were able to study four families in which both parents in each family are group AB. These included two B homozygotes and related persons of widely disparate age. The genotypes and ages of the persons studied are shown in the figure captions. The experiments indicate, first, that non-A and non-B cell proportions in AB children are rather similar to those in adults; second, that the proportions of non-B cells in the B homozygotes, although from 1/5 to 1/20 of those in related heterozygotes, were still from 50 to 200 times higher than the squares of the proportions in the heterozygotes.

The proportions of non-A and non-B cells were estimated by the isotope dilution method previously described (*2*). Saline suspensions of the cells were labeled with Cr^{51} and passed through repeated agglutinations and separations (stages) in the presence of unlabeled "carrier" cells. Within five or six stages the rate of removal of labeled cells per stage usually becomes negligible and the remaining proportion of labeled cells approximates the true inagglutinable fraction. In the present experiments, unlike those previously reported, human anti-A and anti-B sera were used, rather than lima bean anti-A lectin. The sera were obtained from donors selected for the production of commercial typing sera, unselected sera having proved unsatisfactory. In all experiments with anti-B, B cell carrier was used, whereas A_1 carrier was used in all those with anti-A.

Isotope dilution curves with anti-B were obtained for the AB and B persons in three of the families (Fig. 1). The AB persons show no consistent age effect. The results in family II suggest the possibility of a non-B frequency characteristic of the B allele, with Br.O. having received his mother's B allele and Wa.O. his father's. This interpretation does not find further support in family III, nor in the non-A proportion in family II; we regard the result as fortuitous. The B homozygotes are distinct; De.O. has a non-B frequency 10 to 20 times lower than in sibs and parents, and Ka.F. has 5 to 10 times lower.

The results with anti-A are shown in Fig. 2. Evidently the proportions of non-A and non-B cells can be quite

different in the same AB individual. Again, no age effect is apparent. Families I and IV involved AB bloods inagglutinable by anti-A_1, but partially agglutinable by anti-A, a high proportion of free cells being evident on slide tests. These individuals are phenotypically A_3B, but the genotypes are questionable because the A_2B genotype has been reported, in certain pedigrees, to yield a phenotype resembling A_3B (*3*). For our present purposes the subgroup allele will be provisionally called A_3. In family I the result with Ch.N. was technically unsatisfactory, but the subgroup individuals appear to show different isotope dilution curves. In family IV the A_3B phenotypes are remarkably constant. The inagglutinable frequencies in the A_1A_3 persons (in contrast to those in B homozygotes) are quite consistent with independent behavior of the alleles; that is, they approximate the product of the non-A proportions in the A_1B and A_3B persons. The similarity of phenotypic expression of the A subgroup allele in family IV, whether in the presence of the B allele or in the minor cell population that has lost A_1, suggests that in this instance it is appropriate to designate the subgroup allele as A_3.

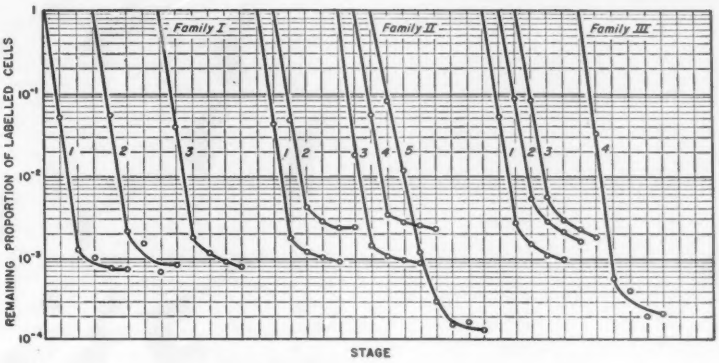

Fig. 1. Isotope dilution curves with anti-B; key:

Family	*Subject*	*Age (yr)*	*Sex*	*Genotype*
I	1, Ch.N.	(adult)	M	A_2B?
	2, C.N.	(adult)	F	A_1B
	3, Ma.N.	1	M	A_2B?
II	1, I.O.	49	M	A_1B
	2, H.O.	47	F	A_1B
	3, Wa.O.	21	M	A_1B
	4, Br.O.	8	M	A_1B
	5, De.O.	14	M	BB
III	1, Ke.F.	10	M	A_1B
	2, A.F.	32	F	A_1B
	3, W.F.	36	M	A_1B
	4, Ka.F.	12	M	BB

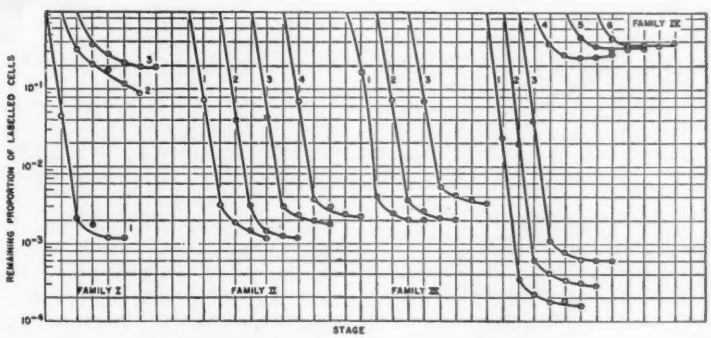

Fig. 2. Isotope dilution curves with anti-A; key:

Family	*Subject*	*Age (yr)*	*Sex*	*Genotype*
I	1, C.N.	(adult)	F	A_1B
	2, Ch.N.	(adult)	M	A_2B?
	3, Ma.N.	1	M	A_2B?
II	1, Br.O.	8	M	A_1B
	2, Wa.O.	21	M	A_1B
	3, H.O.	47	F	A_1B
	4, I.O.	49	M	A_1B
III	1, W.F.	36	M	A_1B
	2, A.F.	32	F	A_1B
	3, Ke.F.	10	M	A_1B
IV	1, D.S.	5	F	A_1A_3
	2, M.S.*	4	M	A_1A_3
	3, P.S.	25	F	A_1B
	4, L.S.*	4	F	A_3B
	5, R.S.	2	M	A_3B
	6, W.S.	28	M	A_3B

* M.S. and L.S. are dizygotic twins.

These results do not exclude an age effect, but they show that an age-independent component is preponderant. Two age-independent sources of mutant cells can be imagined: first, mutant stem lines established early, perhaps during the prenatal period, and second, mutations occurring in the clones that intervene between the stem lines and the erythrocytes. The mutational hypothesis now requires the assumption that mutant cells arising from either or both of these sources greatly outnumber those that arise from the accumulation of mutant stem lines during postnatal life.

The results with the B homozygotes present further difficulties for the mutational hypothesis, since statistically independent events in the two B alleles can account for only a minor fraction of the cells that have apparently lost the B phenotype. It would be necessary to assume that the mutations in homozygous cells are highly correlated, or that genotypic selection has altered the stem cell populations in the required manner, or that a large proportion of exceptional cells in homozygotes are cell phenocopies. The presence of exceptional cells in homozygotes and the inequality of non-A and non-B proportions in AB persons is evidence against somatic segregation (*4*) as a major cause of automosaicism. Finally, the magnitude of the difference in exceptional cell proportions between homozygote and heterozygote suggests that the isotope dilution method may permit determination of homozygote frequencies in population surveys.

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New Source of the j_2 Gene Governing Jointless Pedicel in Tomato

Abstract. A multiple-flowered, jointless pedicel, single plant appeared in the tomato variety 146 in 1958. The gene governing the jointless pedicel character was found to be identical with the j_2 gene found in a tomato strain from the Galapagos Islands. The character is considered to be a mutant and of potential value in the development of mechanically harvestable tomatoes.

An off-type, single plant of the tomato variety 146 (*1*), with multiple flower clusters, was found in a commercial field in 1958. Plants grown in 1959 from seed of this plant produced flower clusters with jointless pedicels. The clusters were bifurcate, differing from those of plants with the j_1 gene (*2*). They were similar in appearance to the jointless pedicel clusters of strain LA 315 received from C. M. Rick. Strain LA 315 was derived from LA 166, a collection of *Lycopersicon pimpinellifolium* from Indefatigable Island of the Galapagos Island group (*3*). The jointless pedicel character of strain LA 315 was reported by Rick to be different from that determined by the gene j_1 and was assigned the symbol j_2 (*3*, *4*). As far as we know this has been the only report of the j_2 gene.

A series of crosses was made between the 146 selection and normal jointed, jointless j_1 type, and jointless j_2 type, using LA 315 for the last cross, with the results shown in Table 1.

Crosses 1, 2, and 3 indicated that 146 selection pedicel type was recessive to normal jointed, was conditioned by a single factor, and was like j_2 pedicels in appearance. Crosses 4, 5, and 6 indicated that 146 selection was not identical with jointless j_1, because the F_1 was jointed, both jointless types appeared in the F_2, and the two backcross populations were distinct, each approaching 1 : 1 ratios for jointed and jointless, with the backcross parent pedicel type only represented.

Crosses 7, 8, and 9 established the identity of the j_2 gene for jointless pedicel in 146 selection and LA 315, with all populations having j_2 pedicels.

In contrast with clusters of 1 to 6 flowers in most j_1 tomato strains or varieties, the j_2 clusters, as grown at Riverton, New Jersey, have from 7 to 30 or more flowers per cluster, although actual fruit set is usually 1 to 4 per cluster. The 146 selection differs from LA 315 in lacking the large and leaflike calyces and the ovoid fruit described for the latter (*3*, *4*). The character behaves normally in crosses and has been combined with both determinate, *sp* and dwarf, *d* characters and with the double recessive, *d*, *sp*. Germination of seed is normal.

The jointless pedicel character results in a minimum of stems remaining on picked ripe fruit. This characteristic may be useful in the development of mechanically harvestable tomato varieties (*5*).

The origin of the j_2 character in 146 is unknown. The LA 315 j_2 was not grown in local experimental plantings until 1960, whereas the 146 selection appeared in 1958. This eliminates the possibility that a chance field pollination from LA 315 introduced the gene to the 146 variety.

Table 1. Classification of tomato plants for pedicel type.

Cross	Parent plants	Generation	No. of plants of phenotype		
			Jointed	Jointless j_1 type	Jointless j_2 type
1	146 sel. × Jointed	F_1	11	0	0
1	146 sel. × Jointed	F_2	72	0	16
2	146 sel. F_1 × Jointed	BC1	41	0	0
3	146 sel. F_1 × 146 sel.	BC1	12	0	10
4	146 sel. × Jointless j_1	F_1	6	0	0
4	146 sel. × Jointless j_1	F_2	18	3	1
5	146 sel. F_1 × Jointless j_1	BC1	13	7	0
6	146 sel. F_1 × 146 sel.	BC1	12	0	10
7	146 sel. × LA 315 j_2	F_1	0	0	4
7	146 sel. × LA 315 j_2	F_2	0	0	46
8	146 sel. F_1 × 146 sel.	BC1	0	0	21
9	146 sel. F_1 × LA 315 j_2	BC1	0	0	22

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7 August 1961

Sources and Isotopic Composition of Atmospheric Sulfur

Abstract. In nonindustrial areas the prime source of SO_4^{--} in rain and snow is atmospherically oxidized H_2S that is produced predominately along coastal belts by anaerobic bacteria. The δ S^{34} analyses of atmospheric SO_4^{--} vary from +3.2 to +15.6 per mil in contrast to +20.7 per mil for sea water SO_4^{--}. Contrary to previous studies based on Cl^-/SO_4^{--} ratios, sea spray SO_4^{--} is a minor source.

Studies on the relationship between variations in isotopic composition of sulfur and the genesis of sulfide minerals (*1*) have led us to encounters with the complexities of the biogeochemical cycle of sulfur. One significant portion of this cycle is the role of sulfur in the atmosphere.

Sulfur occurs in the atmosphere predominately, if not exclusively, as SO_4^{--} in aerosols and in SO_2 and H_2S gas. The second form, and in all probability the third, is oxidized to SO_3, which in the presence of moisture subsequently forms hygroscopic SO_4^{--} nuclei. The SO_4^{--} in aerosols is returned to the earth in precipitation of rain and snow—in variable concentrations between essentially 1 to 10 mg of SO_4^{--} per liter of precipitation.

Three sources for SO_4^{--} in the atmosphere have been suggested. The first and most obvious source, especially to urbanites, is industrial SO_2, which, as shown by Junge (*2*), is certainly quantitatively insufficient to account for the total amount of SO_4^{--} in the atmosphere. The second source is H_2S produced by anaerobic

bacteria existing in marshes, soil, and lakes and, most important of all, along coastal plains and shelves (*3*). The third source is nonhygroscopic particles of sulfate derived from sea spray (*4*); it has been suggested that SO_4^{--} in particles derived from sea spray forms a stable aerosol that is spread throughout the earth's atmosphere while soluble chlorides that enter the atmosphere by the same process are returned rapidly to the sea.

Nevertheless, not only has the relative importance of these three sources been extremely difficult to ascertain, but skepticism has been expressed about the efficacy of the sea-spray process. In 1953 Hutchinson (*5*, p. 421) noted that information on the isotopic composition of sulfur in rain water "should throw light on this subject." The basis for his statement was that sea-water sulfate has a remarkably constant isotopic composition for sulfur. The S^{32}/S^{34} isotopic ratio is 21.76 ± 0.01 or the δ S^{34} enrichment is +20.7 per mil compared to the meteoritic standard of 22.21 for isotopic studies of sulfur (*6*). If sea spray is an important source of SO_4^{--} in aerosols, the δ S^{34} composition of SO_4^{--} collected from precipitation should be essentially +20 per mil since very little, if any, isotopic fractionation is expected during the transfer of the SO_4^{--} from the sea spray to the atmosphere.

Östlund (*7*) recently published the first isotopic analyses of sulfur from SO_4^{--} collected from snow and rain. He also included three isotopic analyses of sea water SO_4^{--}. The sea water analyses he reported are obviously in error as the S^{32}/S^{34} ratios are too high. If the abnormal values are only a question of sulfur isotope standards, which is most likely, these analyses can be salvaged by applying a correction factor of −0.12, as suggested by Östlund (*8*), to all of the S^{32}/S^{34} analyses. This has been done for Östlund's samples listed in Table 1. These corrected values still verify his conclusion that "the sulfate sulfur in precipitation is not likely to originate principally from sea-water spray."

We also concur in this conclusion, on the basis of our analyses of Japanese samples, provided by Ken Sugawara, as listed in Table 1. In addition, however, we have also noted that the SO_4^{--} samples collected by Sugawara from industrial locations are more highly enriched in S^{32} than the samples collected from nonindustrial sites near the western coast of Japan. Although these latter samples do more closely approach the sulfur isotopic composition of SO_4^{--} from the China Sea (Table 1), they are, even so, still enriched by about 5 per mil in S^{32}.

This enrichment is quite typical (*9*) of the isotopic fractionation to be expected by reduction of SO_4^{--} by anaerobic bacteria of the *Desulfovibrio* genus and the resulting evolution of H_2S. Although these coastal samples may still contain SO_4^{--} derived from sea spray, the isotopic analyses indicate that H_2S of biogenic origin, produced in tidal flats and coastal belts, is the prime source of atmospheric SO_4^{--}. Continental and fresh-water environments for the sulfate reducers are unimportant sources of H_2S, as is indicated by the S^{32}-enriched lake water analyses shown in Table 1.

Our isotopic analyses of Sugawara's samples collected from industrial sites exhibit δ S^{34} compositions similar to all of Östlund's SO_4^{--} precipitation samples. It is suggested, of course, that these samples contain SO_4^{--} derived predominantly from atmospheric oxidation of SO_2 of industrial origin. If the δ S^{34} composition of industrial fuels were uniform, it would be possible to determine quantitatively the specific amounts and sources of atmospheric SO_4^{--}. Analyses, however, of just five samples of Japanese coal (Table 1) indicate the relatively broad spread in their isotopic composition of sulfur. The nu-

Table 1. Isotopic composition of sulfur in industrial coal and sea, lake, and atmospheric sulfate.

Sample location	Sample	Sample content (mg SO_4^{--} per liter)	Sample content* (percent by weight)	Isotopic data	
				δ S^{34} (per mil)	S^{32}/S^{34}
		Östlund samples†			
Stockholm, Sweden	Snow	1.5		+5.4	22.09
Stockholm, Sweden	Snow	4.0		+6.8	22.06
Köping, Sweden‡	Rain	3.2		+8.2	22.03
Stockholm, Sweden	Rain	7.9		+3.2	22.14
Stockholm, Sweden	Rain	18.8		+5.0	22.10
Stockholm, Sweden	Rain	7.2		+4.5	22.11
Stockholm, Sweden	Rain	5.1		+3.6	22.13
Stockholm, Sweden	Rain	6.1		+6.8	22.06
Stockholm, Sweden	Rain	9.5		+6.8	22.06
Huddinge, Sweden	Rain	5.3		+6.8	22.06
Huddinge, Sweden	Rain	2.8		+6.3	22.07
Flahult, Sweden	Rain	7.6		+7.3	22.05
Port Aransas, Tex.§	Rain			+6.3	22.07
Nahcotta, Wash.§	Rain			+5.4	22.09
Arctic Sea	Seawater	2740.		+20.2	21.77
North Sea	Seawater	2170.		+19.7	21.78
Gulf of Bothnia, Baltic Sea	Seawater	450.		+20.7	21.76
Lake Mälaren	Lake water	47.		+2.7	22.15
		Sugawara samples			
Tokyo(A), Japan ‖	Rain	8.9		+7.3	22.05
Tokyo(B), Japan ‖	Rain	8.6		+7.3	22.05
Tokyo(C), Japan ‖	Rain			+5.0	22.10
Nagoya(B), Japan ‖	Rain	2.3		+5.9	22.08
Nagoya(C), Japan ‖	Rain			+3.2	22.14
Wakayama, Japan¶	Rain	3.5		+7.3	22.05
Nara, Japan¶	Rain	1.3		+6.3	22.07
Kurume(A), Japan**	Rain	3.0		+15.6	21.88
Kurume(B), Japan**	Rain	2.1		+12.8	21.93
Kurume(C), Japan**	Rain			+15.6	21.88
Tottori(A), Japan**	Snow	2.7		+13.2	21.92
Tottori(B), Japan**	Rain	2.3		+15.1	21.88
Matsumoto, Japan	Rain			+12.3	21.94
Wakayama, Japan	Seawater			+20.7	21.76
East China Sea	Seawater			+20.7	21.76
		Nakai samples			
Long Island Sound, Conn. (surface)	Seawater	2170.		+20.2	21.77
Long Island Sound, Conn. (7-m depth)	Seawater	2170.		+20.2	21.77
Linsley Pond, Conn. (surface)	Lake water	10.2		+7.7	22.04
Linsley Pond, Conn. (13.5-m depth)	Lake water	9.6		+7.3	22.05
Queechy Lake, Conn. (12-m depth)	Lake water	13.8		+7.3	22.05
Kyushu, Japan	Coal		1.54	+23.5	21.70
Kyushu, Japan			1.44	+23.9	21.69
Kyushu, Japan	Coal		3.05	+11.9	21.95
Kyushu, Japan			3.14	+11.9	21.95
Kyushu, Japan	Coal		1.49	+22.1	21.73
			1.48	+22.6	21.72
Hokkaido, Japan	Coal		0.33	+18.3	21.81
Hokkaido, Japan	Coal		0.35	+15.1	21.88

* Determined by Parr Bomb method. † Östlund's isotopic data have been corrected by subtracting 0.12 from ratio values. ‡ Köping is located near Lake Mälaran. § Coastal locations, U.S. ‖ Industrial sites. ¶ Near industrial sites. ** Nonindustrial sites.

merous atmospheric SO_4^{--} samples collected near industrial sites, all of which have S^{32}/S^{34} ratios in excess of 22.03, indicate that the two Japanese coal samples enriched in S^{34} are atypical. Certainly many more δ S^{34} analyses of sulfur in industrial fuels are needed.

It is interesting to note that Junge (*2*) and Eriksson (*10*), using identical data for the concentration of excess SO_4^{--} in precipitation over the United States, have suggested a decrease and an increase, respectively, of excess SO_4^{--} near the coast line. It seems apparent, therefore, that δ S^{34} studies would assist these investigators. In nonindustrial areas, however, the limited present data indicate that H_2S of biogenic origin is the major source of atmospheric SO_4^{--} (*11*).

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13 September 1961

Photoperiodic Response of Female Fringe-Toed Lizards

Abstract. *Uma notata* females were held over the winter under 24 hours of light per day. These animals laid from two to four clutches of eggs, with 4 to 7 weeks between clutches. Clutches contained two to four eggs. Additional light is believed to be more important than heat in causing this response.

Recently Farner (*1*) reviewed the present status of photoperiodicity in the animal kingdom, and Bartholomew (*2*) reviewed photoperiodism in reptiles. Both stated that knowledge of the photoperiodic response in reptiles is extremely limited. Most of what is known concerns males, although Bartholomew (*3*, *4*) studied *Xantusia vigilis* females in this regard. However, he found that ovaries in this species reacted to a much smaller degree than testes (*4*). To my knowledge, no one has reported any female reptile ovulating in response to light stimulation. Consequently, the following observations seem worthy of note.

Table 1. Egg-laying by *Uma notata* in response to light stimulation, 1960–61.

Data	Animal No. 1	Animal No. 2	Animal No. 3
Snout-vent length at 1st clutch (mm)	70	71	76
Date exposed to 24 hr of light per day	20 July	20 July	23 Nov.
1st clutch			
Date	10 Nov.	22 Nov.	24 Jan.
No. eggs	2	2	2
2nd clutch			
Date	9 Dec.	21 Dec.	26 Feb.
No. eggs	3	4	2
3rd clutch			
Date	27 Jan.	12 Feb.	
No. eggs	3	3	
4th clutch			
Date	8 Mar.		
No. eggs	3		
Autopsy date	12 June	10 Apr.	21 Mar.
Condition at autopsy			
Left ovary	6 eggs, 1 large (7.4 mm)	3 eggs, largest 1.0 mm	6 eggs, 1 large (13.7 mm)
Right ovary	6 eggs, 1 large (7.2 mm)	0 eggs	6 eggs, 1 large (12.3 mm)

Fringe-toed lizards (*Uma notata*) are abundant in the Algodones Dunes, Imperial County, California. Females lay eggs in the field from April through August, and lay from one to four eggs in a clutch (*5*). The number of clutches per individual each year is unknown, however. These animals normally hibernate beneath the sand from November to February (*5*).

On 20 July 1960, two subadult females, which had been captured 2 days earlier in the Algodones Dunes, were placed in a small terrarium (12½ by 12½ by 24 inches). A 60-watt incandescent light bulb illuminated and heated the terrarium from above, 24 hours per day. Approximately 2 inches of sand covered the bottom of the cage. Sand surface temperatures in the terrarium ranged from 26.2°C to 29.4°C, depending on the sand's location in relation to the light bulb. Surface temperatures did not vary during the period under consideration.

These animals burrowed in the sand a good deal. Thus, they were not exposed to the light for 24 hours each day. It is impossible to say how many hours of light each animal received, since this was determined by the animal's behavior.

On 10 November lizard No. 1 laid its first clutch of eggs, followed about 2 weeks later by animal No. 2 (see Table 1). Both animals possessed bright reddish-orange sides at the time of laying. This color pattern was identical with that seen in the field on adults of both sexes from May to September (*5*). The laboratory animals, at the time of laying, were about the minimum size (snout-vent length) for laying females in the field (*5*).

On 23 November lizard No. 3, which was approximately the same size, was placed in the terrarium. This female had been hibernating in an outdoor cage as part of another experiment. It did not respond to the light or warmth in any manner until 12 December. Then it began to move about and eat. By 14 December it was beginning to acquire the reddish-orange patches on the sides of the abdomen and by 3 January 1961 its sides were bright reddish-orange. It laid its first clutch of eggs 2 months after it was placed in the terrarium. Table 1 summarizes the egg-laying data for the three animals and gives an indication of ovary conditions at autopsy.

The first and second clutches were approximately 4 weeks apart in all animals. Both lizards that produced a third clutch did so about 7 weeks after they produced the second. The single fourth clutch was laid almost 6 weeks later than the third. Thus, the interval between specific successively numbered clutches was about the same for all animals, but the time between an individual's clutches was rather variable. The eggs laid by these lizards averaged 20.2 by 11.7 mm in size (range, 17.5 by 10.0 mm to 24.0 by 13.1 mm). This compares very closely to the average size of eggs found in the oviducts

of newly captured females of this species (20.4 by 11.7 mm) (*5*). Some eggs from each of the captive animals were incubated artificially, but no embryos developed.

Animal No. 3 escaped from the terrarium on 21 March. It was accidentally stepped on and killed. Autopsy revealed it was nearly ready to lay again. Animal No. 2 died of unknown causes. Autopsy showed its right ovary had almost completely disappeared, and the left ovary contained a few very small ova. This led me to think that perhaps females of this species hatch with a given number of primordial ova in the ovaries. When these have been ovulated, the animal becomes reproductively inactive. This idea was supported by the fact that animal No. 1, after laying a fourth clutch in March, stopped laying. It still retained its breeding colors and appeared perfectly healthy, however.

This hypothesis proved incorrect when No. 1 was autopsied 3 months after it laid its last clutch. It possessed as many eggs in each ovary as No. 3 had at death, although No. 1 laid nearly three times as many eggs as No. 3 (see Table 1). One egg in each ovary was quite enlarged, but neither would have been ready to lay for some time.

At present it is impossible to say how much of this response was due to light and how much to heat. Bartholomew (*3, 4*) found that light is more important than heat in producing a reproductive reaction in *Xantusia vigilis*. Probably a similar situation exists in this case, since the surface temperatures to which these animals were exposed are only slightly above the minimum required for their normal activity. When these animals burrowed in the sand they reduced their environmental temperatures still further.

They could also reduce the amount of light received simply by burrowing in the sand. However, the environmental temperatures of the cage never went above the maximum these lizards could tolerate. Therefore they were not forced to burrow under the sand by extreme temperatures, as they normally are in their natural surroundings. Consequently, they tended to stay on the surface longer than they usually do in the field, and thus were exposed to light for relatively long periods (*6*).

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References and Notes

1. D. S. Farner, *Ann. Rev. Physiol.* **23**, 71 (1961).
2. G. A. Bartholomew, in *Photoperiodism and Related Phenomena in Plants and Animals*, R. B. Withrow, Ed. (American Assoc. for the Advancement of Science, Washington, D.C., 1959), p. 669.
3. ———, *Anat. Record* **106**, 49 (1950).
4. ———, *Copeia* **1953**, 45 (1953).
5. Unpublished data in this laboratory.
6. Thanks are due Loree Ostroff for permission to autopsy animals that had been given to her. This research was supported by grant No. G-5480 from the National Science Foundation.

24 July 1961

Interaction between Riboflavin and Rutin

Abstract. Riboflavin-5′-phosphate forms a charge transfer complex with rutin at neutral *p*H in the same manner as it forms one with tryptophan or serotonin, when the system is observed by quantitative spectrophotometry.

Isenberg and Szent-Györgyi (*1*) reported that a strong charge transfer complex of riboflavin-5′-phosphate (RFP) can be produced at neutral *p*H by simple addition of some indoles (for example, tryptophan and serotonin). During studies of the interaction between biologically active natural substances, Nayatani and Yagi (*2*) observed that rutin, a representative flavonoid pigment, had some inhibitory effect upon photolysis of riboflavin. It is possible that a complex can be formed between rutin and riboflavin and that this complex plays some role in the stabilization mentioned above. We report evidence of interaction between RFP and rutin; we used the method of Isenberg and Szent-Györgyi (*1*).

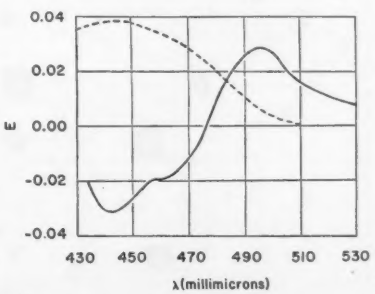

Fig. 1. Absorption curve of RFP-rutin complex in phosphate buffer (*p*H 7.0) at room temperature (solid line). The RFP concentration is $5 \times 10^{-5}M$ in both the sample and the reference cell; the rutin concentration in the sample cell is $2 \times$ [illegible]. The measured extinction is corrected for the rutin absorption. (Dashed line) Absorption curve of a control solution of RFP ($4 \times 10^{-5}M$).

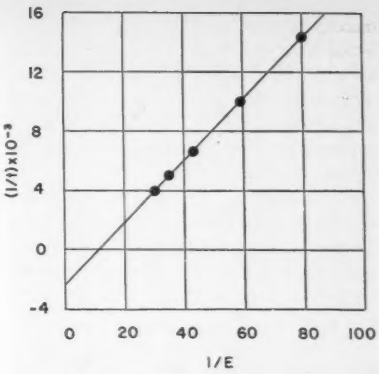

Fig. 2. Plot of the inverse of the rutin concentration ($1/t$) versus the inverse of the extinction of the complex ($1/E$). The RFP concentration is $5 \times 10^{-5}M$ in both cells.

Upon balancing $5 \times 10^{-5}M$ RFP with varying concentrations of rutin against $5 \times 10^{-5}M$ RFP, all in phosphate buffer of *p*H 7.0, a peak was obtained at 495 mμ, while a control solution of RFP showed a peak at 445 mμ (Fig. 1). In the 400- to 530-mμ region, the measured extinction of the complex was corrected for the considerable absorption of rutin. From the similarity of this shift to the shifts in the spectra of RFP and indoles, we concluded that a strong charge transfer complex is produced, in which a rutin molecule gives one electron to an RFP molecule.

To compare rutin's affinity with the indoles' affinity, the inverse of the dissociation constant of the complex, K, was obtained by plotting $1/E$ against $1/t$, as shown in Fig. 2. Since the intercept on the ordinate corresponds to $-K$, rutin's K equals 2400 lit./mole; K for tryptophan equals 60 and K for serotonin equals 400. It is interesting to note that rutin has much higher affinity for riboflavin than tryptophan or serotonin.

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References

1. I. Isenberg and A. Szent-Györgyi, *Proc. Natl. Acad. Sci. U.S.* **44**, 857 (1958); ———, *ibid.* **45**, 1229 (1959); I. Isenberg, A. Szent-Györgyi, S. L. Baird, Jr., *ibid.* **46**, 1307 (1960).
2. K. Nayatani and K. Yagi, *Studies (Kobe College)* **4**, No. 3, 43 (1958).

22 September 1961

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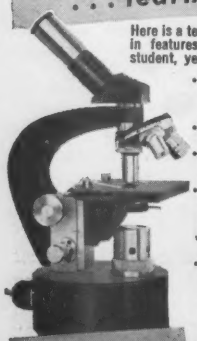

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Meetings

The Nature of the Real

A series of conferences on the nature of the real was held at Marquette University, Milwaukee, Wisconsin, from 12 to 15 June 1961.

Of the six principal speakers, three were physicists and three were philosophers. The physicist speakers were Eugene P. Wigner (Princeton University), Alfred Landé (Ohio State University), and Robert Maurer (University of Illinois). The philosopher speakers were R. J. Henle (St. Louis University), Paul Weiss (Yale University), and Charles DeKoninck (Laval University). Three other philosophers formally commented on the papers of the three physicists and three other physicists commented on the papers of the philosophers. The philosopher commentators were G. Klubertanz (St. Louis University), Richard Blackwell (John Carroll University), and James Weisheipl (Dominican House of Studies). The physicist commentators were Max Dresden (State University of Iowa), Albert Rose (RCA Laboratories), and L. W. Friedrich (Marquette University).

It was pointed out by the physicists that the reason why the problems of epistemology and ontology are of increased interest to the contemporary physicist is that he has found it impossible to give a satisfactory description of atomic phenomena without explicit reference to consciousness. It was suggested by one physicist that there are two kinds of reality: that of my consciousness, which is absolute, and that of other objects, which is relative and ranges over a wide spectrum.

Causality was discussed by both the philosophers and the physicists. Attempts to hold out for cause-effect continuity in all of reality falter when one encounters quantum mechanical interpretations of atomic phenomena. Two of the physicists expressed the fear that their colleagues have become so enthralled by the success of the mental constructs, or concepts, used by physicists that they unwittingly fail to distinguish purely mental concepts from the real world. As an example of this, reference was made to Bohr, who was accused of transferring the uncertainty of prediction expressed by the Heisenberg uncertainty principle into an indeterminacy of being itself, thereby treating the analysis of concepts as though such analysis were equivalent to an examination of primary data.

One of the philosophers explained that we discover physical reality through a primary form of human experience which is at the same time the primary content of human consciousness. This experience is a concrete encounter with a complex object, or set of objects. It is a knowledge encounter as well as an encounter with objects. The physical reality which we discover through continuing encounters is not only a world of existing extended beings; it is a world of movement and change, of interaction and interrelation. Insightful reflection and inference bring us to see that the existence and activity of the physical world must be understood within a framework of causes and of causal explanation.

Another of the philosophers pointed out that scientific study gives us a more objective, precise, and systematic grasp of reality than is obtainable by the commonsense man. Nevertheless, it does not give us the ultimately real. Grasp of ultimate reality is possible "only through speculation, in a dialectically sustained systematic account of the content of common experience, dis[illegible]led and generalized."

It was agreed by most of the participants that, although the vast array of reproducible experiments demonstrates that there are an extraordinarily large number of phenomena that are causally related, yet the causal principal is not valid for all known sequences of phenomena. Some observables remain erratic and unpredictable despite the refined techniques used to measure them. Physicists do not attribute this to the limitations of their techniques. That leaves little choice but to accept, as an ultimate fact of the real world, the absence of causal relation linking these phenomena.

Not much light was cast during these conferences on how the acausal, relatively random, behavior at the atomic level can be the basis for ordered causal behavior at the macroscopic level. It is difficult to determine where the transition (if it can be called that) occurs between random, acausal behavior and ordered behavior, or between a random distribution of elementary particles and an ordered structure of which those same particles become the ultimate components.

The purpose of the conferences was simple and fundamental. They were held to attempt the building of a bridge

of understanding between philosophers and physicists. Until the two groups agree on the meanings of words they use in common and until they accept the scope of each other's valid areas of interest as well as understand each other's limitations, meaningful dialogue between the two is well-nigh impossible.

Recurring efforts were made on the part of many of the participants to outline the "levels of reality" within the entire spectrum of reality, from the most really real down to the most tenuously real. These conferences pointed up the problems involved in such attempts. Much needs to be done before these problems will be solved.

Both the philosophers and the physicists agreed that they must learn much from each other before a good philosophy of physics can be written, if indeed that will ever be possible.

A total of 121 persons attended the conferences. Publication of the proceedings of these conferences is planned.

L. W. FRIEDRICH

Marquette University, Milwaukee, Wisconsin

Forthcoming Events

January

22–24. Institute of the Aerospace Sciences, 30th annual, New York, N.Y. (IAS, 2 E. 64 St., New York 21)

22–26. American Mathematical Soc., annual, Cincinnati, Ohio. (AMS, 190 Hope St., Providence 6, R.I.)

23. Conference on Cardiac and Vascular Surgery, New York Heart Assoc., New York, N.Y. (R. Ober, NYHA, 10 Columbus Circle, New York 19)

23–25. American Soc. of Safety Engineers, Philadelphia, Pa. (A. C. Blackman, 5 N. Wabash Ave., Chicago 2, Ill.)

23–25. Obstetrics and Gynaecology, 2nd Asiatic congr., Calcutta, India. (S. Mitra, 4 Chowringhee Terrace, Calcutta 20)

24–26. Mathematical Assoc. of America, 45th annual, Cincinnati, Ohio. (H. M. Gehman, Univ. of Buffalo, Buffalo, N.Y.)

24–26. Thermophysical Properties, symp., American Soc. of Mechanical Engineers, Princeton, N.J. (E. F. Lype, ASME, c/o Thompson Ramo Wooldridge, 23555 Euclid Ave., Cleveland, Ohio)

24–27. American Physical Soc., annual, New York, N.Y. (K. K. Darrow, 538 W. 120 St., New York 27)

24–27. Federation of American Scientists, Natl. Council, New York, N.Y. (D. M. Singer, FAS, 1700 K St., NW, Washington 6)

25–26. Western Spectroscopy Assoc., 9th annual, Pacific Grove, Calif. (D. G. Rea, WSA, Univ. of California Space Sciences Laboratory, Berkeley 4)

25–27. Western Soc. for Clinical Research, 15th annual, Carmel-by-the-Sea, Calif. (H. R. Warner, WSCR, Latter-Day Saints Hospital, Dept. of Physiology, Salt Lake City 3, Utah)

26–29. Man and Civilization: Control of the Mind—II, San Francisco, Calif. (S. M. Farber, Univ. of California San Francisco Medical Center, San Francisco 22)

28–3. American Inst. of Electrical Engineers, New York, N.Y. (R. S. Gardner, AIEE, 33 W. 39 St., New York 18)

28–3. Pan American Assoc. of Ophthalmology, interim congr., Lima, Peru. (J. M. McLean, 525 E. 68 St., New York 21)

29–30. Carbohydrates, Cellulose, and Cellulose Industries, symp., Council of Scientific and Industrial Research, Ahmedabad, India. (Director, Ahmedabad Textile Industry Research Assoc., Ahmedabad-9)

29–31. American Soc. of Heating, Refrigerating and Air-Conditioning Engineers, St. Louis, Mo. (R. C. Cross, United Engineering Center, 345 E. 47 St., New York, N.Y.)

29–31. Institute of the Aeronautical Sciences, annual, New York, N.Y. (R. R. Dexter, IAS, 2 E. 64 St., New York 21)

29–1. Instrument Soc. of America, conf. and exhibit, Dallas, Texas. (W. H. Kushnick, ISA, 313 Sixth Ave., Pittsburgh 22, Pa.)

30–1. Military Electronics, 4th winter convention, Institute of Radio Engineers, Los Angeles, Calif. (IRE, 1435 LaCienega Blvd, Los Angeles)

30-2. Society of Plastics Engineers, annual technical conf., Pittsburgh, Pa. (T. A. Bissell, SPE, 65 Prospect St., Stamford, Conn.)

31–2. American Geophysical Union, Pacific Southwest regional, Tucson, Ariz. (A. N. Sayre, U.S. Geological Survey, Washington 25)

February

1–2. Industrial Management Engineering Conf., Illinois Inst. of Technology, Chicago. (F. A. Judd, Technology Center, IIT, Chicago 18)

1–3. Congress on Hospital Administration, 5th annual, Chicago, Ill. (American College of Hospital Administrators, 840 N. Lake Shore Dr., Chicago)

4–7. American Inst. of Chemical Engineers, natl., Los Angeles, Calif. (American Petroleum Inst., 1271 Avenue of the Americas, New York 20)

5. World Meteorological Organization, Working Group on Networks of the Commission for Synoptic Meteorology, Geneva, Switzerland. (Secretary, WMO, Geneva)

5–6. Gustav Stern Symp. on Perspectives in Virology—III, New York, N.Y. (M. Pollard, Lobund Inst., Univ. of Notre Dame, Notre Dame, Ind.)

5–7. American Acad. of Allergy, annual, Denver, Colo. (Scientific Liaison Office, Natl. Research Council, Sussex Dr., Ottawa, Ont., Canada)

5–9. Electroforming Applications, symp., American Soc. for Testing and Materials, Dallas, Tex. (ASTM, 1916 Race St., Philadelphia 3, Pa.)

6–7. Vertebrate Pest Control Conf., Sacramento, Calif. (M. W. Cummings, Univ. of California, Davis)

6–8. Society of the Plastics Industry, Re-

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inforced Plastics Div., Chicago, Ill. (Scientific Liaison Office, Natl. Research Council, Sussex Dr., Ottawa, Ont., Canada)

7–9. Military Electronics, Inst. of Radio Engineers, Los Angeles, Calif. (M. E. Brady, Space Technology Laboratories, P.O. Box 95001, Los Angeles)

7–10. American College of Radiology, annual, New York, N.Y. (ACR, 20 N. Wacker Dr., Chicago 6, Ill.)

8. Problems in Food Processing, Assoc. of Vitamin Chemists, Chicago, Ill. (H. S. Perdue, Abbott Laboratories, N. Chicago)

8. Tissue Homotransplantation, 5th biennial conf., New York, N.Y. (W. Dameshek, New England Center Hospital, 171 Harrison Ave., Boston 11, Mass.)

9–11. National Open Hearth and Blast Furnace Conf., American Inst. of Mining, Metallurgical, and Petroleum Engineers, Detroit, Mich. (E. O. Kirkendall, AIME, 29 W. 39 St., New York 17)

12–16. Management of Science Information Centers, Inst. on Information Storage and Retrieval, 4th, Washington, D.C. (L. H. Hattery, Center for Technology and Administration, American Univ., 1901 F St., NW, Washington 6)

12–23. Latin American Seminar on Irrigation, 2nd, Panama City, Panama. (J. Melendez, Jefe, Depto. de Ingenieria, Ministerio de Agricultura, Comercio e Industrias, Panama City)

13–14. Sanitary Engineering, 4th conf., Urbana, Ill. (B. B. Ewing, Dept. of Sanitary Engineering, Univ. of Illinois, Urbana)

14–16. Biophysical Soc., 6th annual, Washington, D.C. (D. Cowie, Dept. of Terrestrial Magnetism, Carnegie Institution of Washington, 5241 Broad Branch Rd., NW, Washington 15)

14–16. Solid State Circuits, intern. conf., Philadelphia, Pa. (L. Winner, 152 W. 42 St., New York 36)

14–17. National Soc. of College Teachers of Education, Chicago, Ill. (E. J. Clark, Indiana State College, Terre Haute)

16–18. Medical Congr. in Honor of the Centennial of Bretonneau, Tours, France. (Directeur, École Nationale de Médecine, Tours)

17–24. Pan American Medical Women's Alliance, 8th congr., Manizales, Colombia. (C. Carthers, 1661 Riverside Ave., Suite B, Jacksonville, Fla.)

18–22. American Inst. of Mining, Metallurgical, and Petroleum Engineers, annual, New York, N.Y. (E. O. Kirkendall, AIME, 29 W. 39 St., New York 17)

18–22. Technical Assoc. of the Pulp and Paper Industry, annual, New York, N.Y. (TAPPI, 360 Lexington Ave., New York 17)

19–21. American Educational Research Assoc., Atlantic City, N.J. (G. T. Buswell, 1201 16 St., NW, Washington 6)

19–21. Tracking and Command of Aerospace Vehicles, Inst. of the Aerospace Sciences, San Francisco, Calif. (IAS, 2 E. 64 St., New York 21)

19–22. American Concrete Inst., annual, Denver, Colo. (W. A. Maples, 22400 W. Seven Mile Rd., P.O. Box 4754, Redford Station, Detroit 19, Mich.)

19–22. Industrial Ventilation Conf., E. Lansing, Mich. (Engineering Dept., Michigan State Univ., E. Lansing)

19–23. American Soc. of Civil Engineers, Houston, Tex. (W. H. Wisely, 345 E. 47 St., New York 17)

19–23. Automatic Control in the Iron and Steel Industry, intern., Brussels, Belgium. (Institut Belge de Régulation et d'Automatisme, 98 Chausèe de Charleroi, Brussels 6)

20–21. International Inst. of Sugar Beet Researchers, winter congr., Brussels, Belgium. (O. J. Kint, IISBR, 152 rue Beauduin, Tirlemont, Belgium)

21–25. National Assoc. for Research in Science Teaching, Washington, D.C. (H. Branson, Dept. of Physics, Howard Univ., Washington 1)

22–24. American Acad. of Forensic Sciences, Chicago, Ill. (W. J. R. Camp, Univ. of Illinois, 1853 W. Polk St., Chicago 12)

22–24. Genetics Soc. of Canada, Winnipeg, Man., Canada. (Scientific Liaison Office, Natl., Research Council, Sussex Dr., Ottawa, Ont., Canada)

23–24. American Physical Soc., Austin, Tex. (K. K. Darrow, APS, Columbia Univ., New York 27)

23–24. Canadian Aeronautical Inst., mid-season meeting, Halifax, Nova Scotia. (Scientific Liaison Office, Natl. Research Council, Sussex Dr., Ottawa, Canada)

25–1. Pan American Assoc. of Oto-Thino-Laryngology and Broncho-Esophagology, Caracas, Venezuela. (C. M. Norris, 3401 N. Broad St., Philadelphia 40, Pa.)

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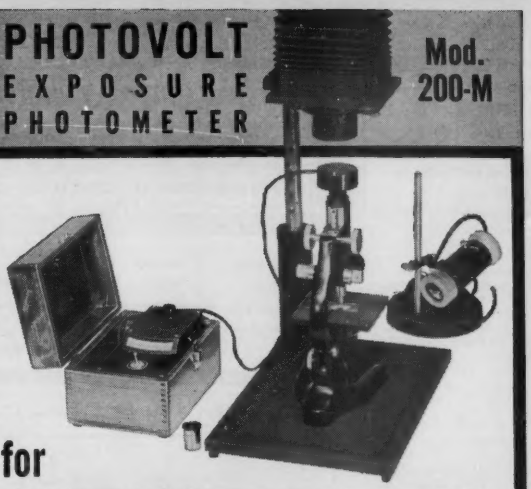

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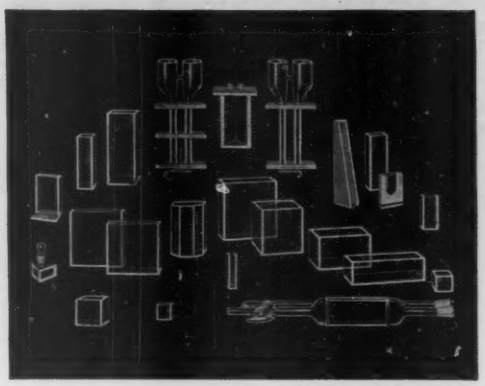

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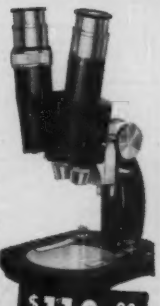

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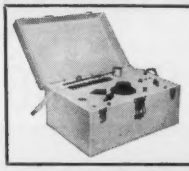

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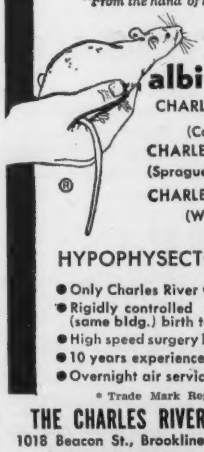

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Measurements of Optical Path Difference With The Dyson Interferometer Microscope

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A. Relation of individual chemical constituents to the total dry mass of the cell and cell organelle.

B. Quantitative data on mass and concentration of substances in nucleoli, chromosomes, fibrils, etc.

C. Cell growth, as shown by dry mass measurements at regular intervals.

D. Change in concentration and distribution of dry mass during physiological processes, such as muscle contraction, vacuole function, cell locomotion; or due to disease, cellular differentiation, protein secretion, etc.

E. Measurement of substance removed, if cell or tissue is fixed and extracted with chemical reagents or digested with enzymes.

F. Quantitative estimates of enzyme activity, in terms of rate of production of end-product per unit of dry mass of tissue.

G. Quantitative measurements of mineral salt and organic material in bone and similar materials.

H. Precise refractive index measurements at high powers in chemical material.

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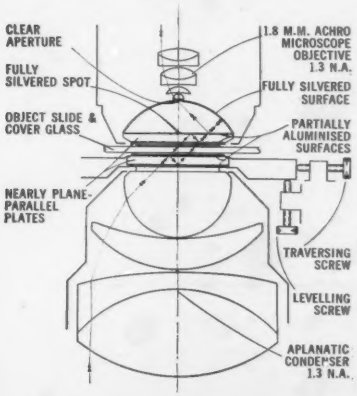

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1. Excellence of definition and contrast at high numerical apertures.
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3. Separation of interference bands can be varied through a wide range — one band can cover the whole field of view or the field may be crossed with several parallel and equidistant bands.
4. By use of the special photometer eyepiece supplied, intensity measurements of an order of accuracy of $\lambda/100$ can be easily made.
5. A modern stand with built-in magnification changer and focusable Bertrand Lens is supplied.

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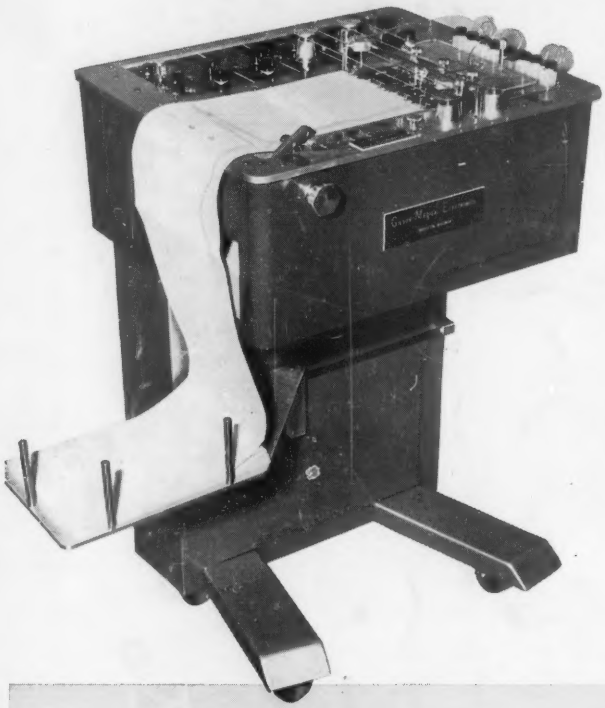

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